The effect of dairy consumption with exercise and healthy eating on the metabolic profile in overweight/obese adolescent girls

by

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ABSTRACT

Childhood obesity is a major health concern. Strategies to reduce this condition, including lifestyle modification with exercise and healthy nutrition, can reduce disease risk. Canada's Food Guide (CFG) recommends a well balanced and healthy diet, however, children and adolescents are not meeting these recommendations, and this too is associated with poorer health. It has been proposed that the intake of dairy products can improve cardiometabolic risk factors in adults. However, research findings are inconsistent for dairy and cardiometabolic variables among adolescents. Therefore, this study aimed to determine the effect of dairy consumption, as part of a 12-week exercise and nutrition program, on fasting serum lipids (total cholesterol, LDL-c, HDL-c, triglycerides), insulin and glucose in overweight (OW) and obese (OB) adolescent girls. Twenty adolescents (10-18 years) were randomly assigned to two groups: recommended dairy (RDa, n=9) or low dairy (LDa, n=11). The RDa group consumed CFG's recommended servings of dairy (4 servings/d), and the LDa group consumed ≤ 1 serving/d (reflecting habitual intakes). All participants followed an exercise program (three 60-minute sessions/wk) and a eucaloric weight management diet. There were no changes in the metabolic profile following the intervention, and no differences were seen between groups. Waist circumference ($p=0.003$) and fat mass ($p<0.001$) decreased and lean mass ($p=0.01$) increased after 12 weeks, with no differences between groups. Significant correlations were seen between body mass change and insulin change, waist circumference change and total cholesterol, insulin and HOMA-IR changes, and QUICKI change and body fat percent change. Further analysis with a larger sample size is required to determine the effect of increased dairy consumption as part of a lifestyle intervention on metabolic variables in OW/OB adolescent populations.

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LIST OF ABBREVIATIONS

ALA – Alpha Linoleic Acid
BMI – Body Mass Index
CCHS – Canadian Community Health Survey
CDA – Canadian Diabetes Association
CDC – Centers for Disease and Control
CLA – Conjugated Linoleic Acid
CSEP – Canadian Society of Exercise and Physiology
CSFII – Continuing Survey of Food Intake by Individuals
CVD – Cardiovascular Disease
FAS – Fatty Acid Synthase
FFAs – Free Fatty Acids
FM – Fat Mass
FR – Food Record
GLUT – Glucose Transporter Protein
HDL-c – High Density Lipoprotein Cholesterol
HOMA-IR – Homeostatic Model Assessment - Insulin Resistance
HSL – Hormone Sensitive Lipase
IDF – International Diabetes Federation
LDa – Low Dairy Group
LDL-c – Low Density Lipoprotein Cholesterol
LPL – Lipoprotein Lipase
MetS – Metabolic Syndrome
NCHS – National Center for Health Statistics
NHANES – National Health and Nutrition Examination Survey
OB – Obese
OW – Overweight
PTH – Parathyroid Hormone
RCT – Randomized Controlled Trial
RDa – Recommended Dairy Group
Sd-LDL – Small Density Low Density Lipoprotein Cholesterol
SSB – Sugar Sweetened Beverages
Svgs/d – Servings/day
T2D – Type 2 Diabetes
TC – Total Cholesterol
TGs – Triglycerides
VLDL – Very Low Density Lipoprotein
TV – Television

CHAPTER 1

INTRODUCTION

Excess weight in children and adolescents is a growing concern across the world. This is mostly due to the comorbidities (e.g., type 2 diabetes, hypertension, metabolic syndrome) which may develop during this time, and may remain into adulthood (1). Some overweight (OW) and obese (OB) children/adolescents present with cardiometabolic risk factors such as reduced high-density-lipoprotein cholesterol (HDL-c), and increased triglycerides (TGs), total cholesterol (TC) and low-density-lipoprotein cholesterol (LDL-c), as well as impaired glucose control (imbalance between insulin and glucose) (2).

Lifestyle modification has been shown to be an appropriate approach to reduce childhood obesity and related disorders (1,3,4). It includes the implementation of regular physical activity, healthy dietary patterns and behavioural change for the child and, preferably, for the entire family (5). A healthy dietary pattern is the consumption of a nutritious, balanced diet containing all food groups in the appropriate amounts according to Canadian Pediatric Guidelines (6), the Academy of Nutrition and Dietetics (7) and Canada's Food Guide (8). Multidisciplinary interventions (combining physical activity, healthy diet and behavioural support) for childhood obesity treatment have been shown to improve cardiometabolic risk factors, such as dyslipidemia, insulin resistance and metabolic syndrome (2,5,9–11).

Dairy foods are excellent sources of macronutrients (protein, carbohydrates, fat) and micronutrients (e.g. calcium and vitamin D) that are important for childhood nutrition because they have been shown to improve several facets of growth and development (12). However, consumption of dairy products is generally low among Canadian youth, with 83% of girls' age 10-16 years not consuming the recommended minimum intake of 3 servings/day (svgs/d) (13). Different studies have suggested that milk and/or dairy product intake is associated with a lower risk of central adiposity in children, adolescents and adults (14,15). However, only a few studies have investigated the relationship between dairy intake and cardiometabolic variables, including cross-sectional studies (16–20) and one randomized controlled trial (RCT) (21), in OW and OB children/adolescents. Kelishadi et al. investigated dairy and cardiometabolic risk factors in young, OB children in a RCT (21). They examined different levels of dairy intake in 120 pre-pubertal, OB children (5-6 years old) for 3 years, with the first 6 months involving monthly family-centered educations sessions about healthy lifestyle for all participants, and the remaining 30 months being observational. The participants were assigned to three groups, a dairy-rich diet (>800mg calcium/d) with no change in macronutrient intake (children were advised to consume low-fat and regular milk, yogurt, cheese, solid and liquid curd), a calorie-restricted diet (-500kcal/d; with habitual/no added dairy intake), and a control group (no additional recommendations other than the educational sessions). In all groups, TGs, fasting insulin, HDL-c and homeostatic assessment model insulin resistance (HOMA-IR) improved after the 6-month trial without significant differences between groups (21).

Evidence in adults suggests that dairy foods have a protective effect on cardiometabolic biomarkers mediated by natural dietary components and nutrients

found in dairy such as calcium (22–28), bioactive peptides derived from milk protein (29), and the unsaturated fatty acids present in milk fat (30). These nutrients may improve or, at least, not increase cardiometabolic risk *via* mechanisms relating to the improved satiety response, reduction of body fat and regulation of glucose homeostasis (22,29,30).

It is currently unknown whether exercise training and high dairy consumption, as part of a healthy eating and exercise program can positively affect glucose, insulin and blood lipids in OW/OB adolescent females. It is known that exercise increases energy expenditure and improves cardiometabolic variables in children and adolescents (31,32). However, it is not known whether dairy consumption can affect these metabolic variables in adolescents. Insofar as other variables are concerned, only two studies, in normal weight youth, have investigated dairy consumption (33) or calcium supplementation (34) plus exercise, demonstrating a positive effect on bone mineral density in boys and girls, respectively (33,34), and no effect on body composition (33).

The Improving Diet, Exercise and Lifestyle (IDEAL) for Adolescents Study forms the basis of this thesis. It is a RCT in OW/OB adolescent girls designed to assess the effect of adequate levels of dairy consumption on a background of healthy dietary advice and exercise, with the primary outcomes of bone turnover and body composition. It is similar to a study by Volek et al., who investigated the effects of exercise along with dairy consumption on body composition and bone in male adolescents (13-17 years) (33). Volek et al demonstrated that after 12 weeks of resistance training (3x/week) and milk intake (3 svgs/d), male adolescents had significant improvements in whole body bone mineral density, but not body composition. In addition, the IDEAL Study was also modeled from previous research

by Josse et al., in which increased dairy and protein consumption was investigated along with energy restriction and exercise in OW/OB young women for 16 weeks (35). Participants were divided in three groups, low dairy, medium dairy and high dairy (high protein). They found that the combination of dairy plus a mixed exercise program plus energy restriction induced weight loss and showed significant positive effects on bone health biomarkers and body composition compared to the group without dairy. Cardiometabolic variables were also investigated in this study showing that TGs, TC and LDL-c were significantly reduced in the low dairy and high dairy groups (not in the medium dairy group), and insulin levels were decreased in the medium dairy group. Thus, the IDEAL for Adolescents Study was designed to start to fill the gaps in the literature, and investigate the benefits of exercise with increased dairy primarily on bone health and body composition, and secondarily on cardiometabolic variables. No previous studies have investigated different intakes of dairy as part of a lifestyle modification intervention in OW/OB youth. Therefore, the purpose of this thesis was to investigate whether increased consumption of dairy, as part of a lifestyle modification program including exercise training and healthy eating (diet based on weight maintenance), would affect the metabolic variables in OW/OB adolescent girls after 12 weeks. The current study is the first to use such an approach of lifestyle modification with different quantities of dairy consumption to assess the effect on blood lipids and glucose homeostasis in OW and OB adolescent girls.

CHAPTER 2

REVIEW OF LITERATURE

2.1 CHILDHOOD OVERWEIGHT AND OBESITY

2.1.1 Definition of Overweight and Obesity

The basis for a general definition and diagnosis of OW and obesity is the body mass index (BMI), defined by the calculation of weight in kilograms divided by the height in meters squared (kg/m^2) (36). Specific for children, the Centers for Disease Control and Prevention established growth charts based on sex and BMI-for-age (37); where the child's calculated BMI (kg/m2) is plotted onto the chart with the child's age. The point located on the chart where BMI and age meet is the child's BMI percentile (Figure 1 and Figure 2). The score on the growth chart indicates whether the child is underweight, healthy weight, OW or OB (Table 1)(38). School-aged children and youth (aged 5-19 years) whose BMI is greater than the 85^{th} percentile are considered OW, and those whose BMI is above the 97^{th} percentile are considered OB; younger children (aged 2-5 years) must be over the 97^{th} percentile to be considered OW, and more than the 99.9^{th} percentile to be considered OB (38).

Table 1. BMI percentile classification for children aged 5 to 19 (39)

Classification	**BMI percentile**
Risk for underweight	Below 3^{rd}
Normal weight	3^{th} – 84.9^{th}
Overweight	85^{th} – 96.9^{th}
Obese	97^{th} – 99.8^{th}
Severely obese	Above 99.9^{th}

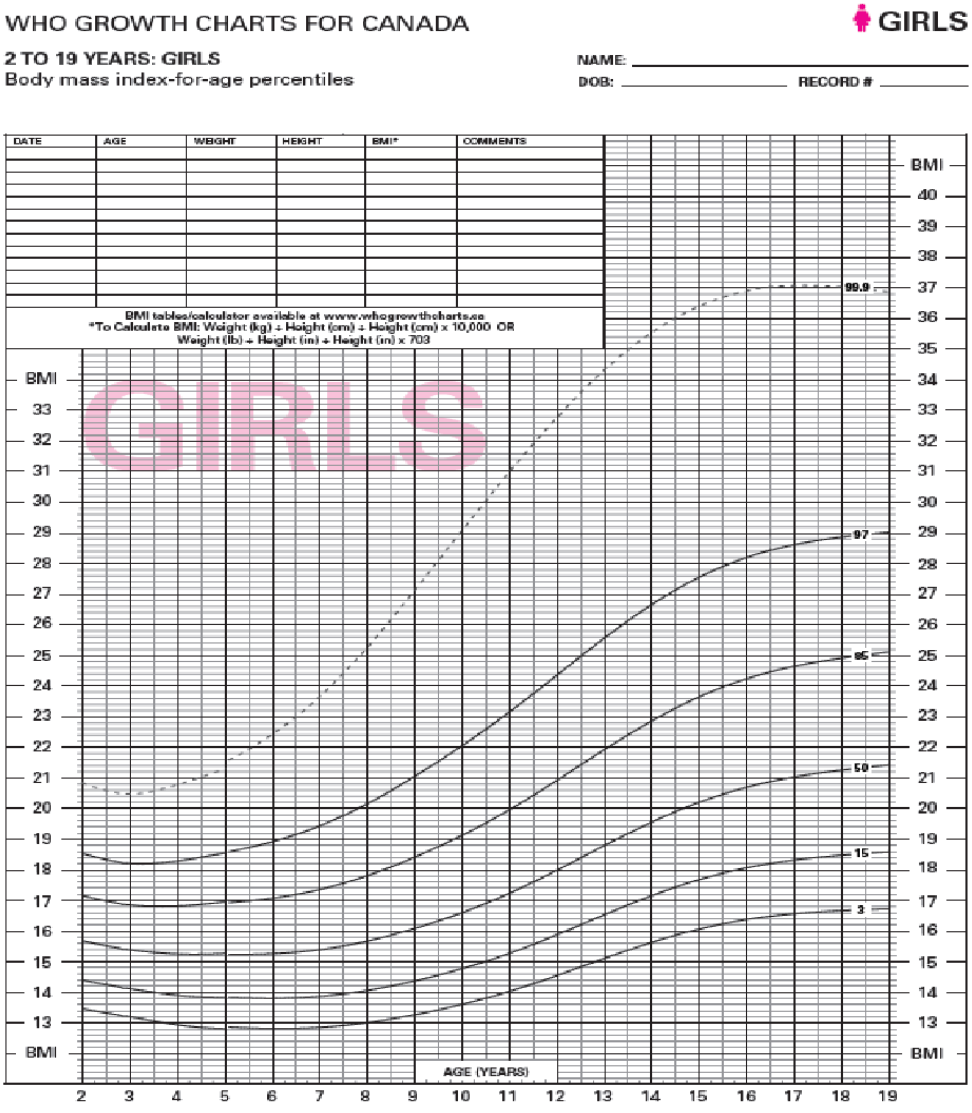

Figure 1. BMI-for-age percentile. 2 to 19 years for girls (25)

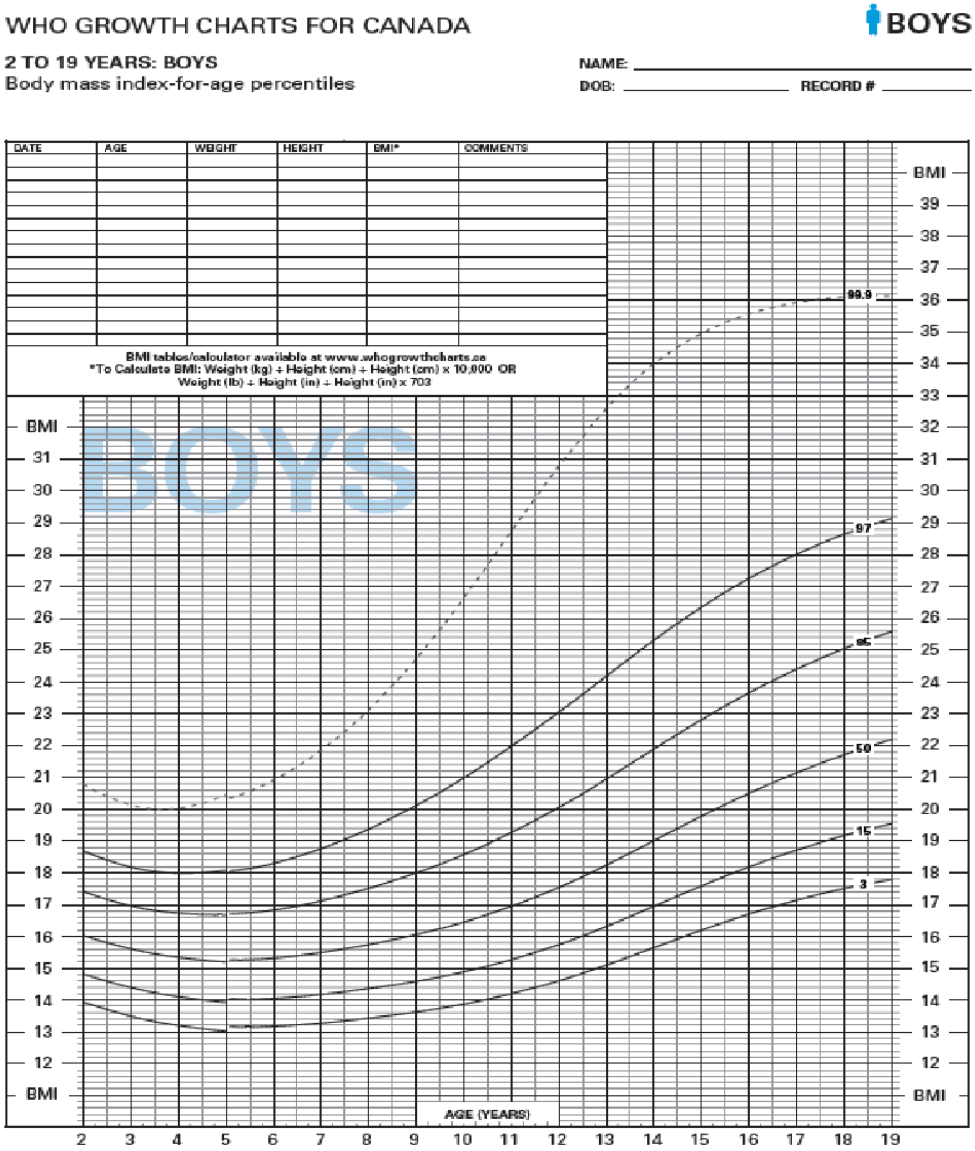

Figure 2. BMI-for-age percentile. 2 to 19 years for boys (26)

2.1.2 Prevalence of Childhood Overweight and Obesity

The prevalence of OW and obesity among children, adolescents and adults worldwide has risen dramatically over the last decade (39). More than 1.9 billion adults (aged 18 years and older) worldwide were classified as OW in 2014. Among these, 600 million adults were classified as OB. According to the National Center for Health Statistics (NCHS), one quarter of Canadian adults are OB, while in the United States, the number is up to one third of the adult population being OB (40). The recent

Canadian Health Measures Survey (2009-2013) reported obesity prevalence among children and adolescents aged 3 to 19 years at 13%. In the United States, the prevalence of obesity among 3 to 19 year olds was reported as 17.5% from 2009 to 2012 (40). According to Peirson et al., almost one-third (31.5%) of the elementary and secondary school-aged children in Canada are OW or OB, indicating that treatment and prevention of childhood obesity should be high priority for Canadian Public Health (41).

Childhood OW/OB prevalence is alarming because metabolic changes and their consequences, normally observed only in the adults, are now observed in younger individuals (42). Its impact on morbidity, mortality and quality of life has made childhood obesity a great public health concern (10). In children and adolescents, obesity is the most common cause of increased cardiovascular risk factors, including dyslipidemia (high plasma TGs and low levels of HDL-c), insulin resistance (impaired insulin-mediated glucose uptake in peripheral tissues) and hypertension (1). Metabolic syndrome (MetS) has also been observed in children, which is characterized by the presence of different combinations of cardiometabolic risk factors including hypertension, impaired fasting glucose, increased TGs, low HDL-c and increased waist circumference (43). The prevalence of MetS among Canadian children and adolescents is 2.1%, which corresponds to approximately 64,832 individuals (44). The prevalence of one or more of these risk factors among Canadian youth is 37.7% (44). The probability of MetS occurrence increases with obesity, and age is one of the most important predictors (45). Thus, children and adolescents with one or more risk factor may be at an increased risk for the development of MetS, thus, increasing their risk for chronic disease as adults (45). According to Johnson et al., the most prevalent risk factors for MetS among youth are

abdominal obesity, increased TGs and decreased HDL-c (46). The International Diabetes Federation (IDF) considers abdominal obesity as a definite prerequisite for MetS given that it is associated with an increased risk of cardiovascular disease (CVD) and an independent predictor of insulin resistance, abnormal lipid concentrations and high blood pressure (47,48).

Childhood obesity, low physical activity, poor fitness level, poor quality diet and cardiometabolic complications are known to track into adulthood and predict premature death (49,50). Thus, successful prevention and treatment of obesity in childhood could reduce the incidence of metabolic disorders in adulthood, thus improving long-term health outcomes in our population (51,52).

2.1.3 Indicators of Overweight/Obesity and Health-Related Factors

Although BMI has been widely used as a screening tool and risk factor for several metabolic conditions that arise because of excess body mass, it should only be considered as an approximate reflection of adiposity (53). BMI is only a calculation of total body mass and height, and it does not distinguish the difference between body fat, muscle and water content (54). Thus, it may be misleading in the classification of children with above-average lean muscle mass, above-average height or with excess body fat leading to obesity (55,56). Childhood health risks can also be assessed by examining body composition. Generally, body composition measures are percent total body fat (%BF), fat mass (FM) (kg) and lean mass (LM) (kg). Body fat for children and adolescents may vary depending on age, sex and pubertal development (57). There is no clear cut-off point of %BF in this age group, however, Rodriguez et al. suggested a range for excess %BF between 30-35% for females and 25-30% for male

adolescents aged 10-15 years, and 20-25% for 16-18 years (58). McCarthy proposed a chart for body fat percentile values by age based on 1,985 Caucasian children aged 5-18 years in the UK showed in Table 2 (57).

Table 2.Tabulated body fat percentile values by exact age (58)

	Centile								
Years	*2*	*9*	*25*	*50*	*75*	*85*	*91*	*95*	*98*
Boys									
5.0	12.2	13.1	14.2	15.6	17.4	18.6	19.8	21.4	23.6
6.0	12.4	13.3	14.5	16.0	18.0	19.5	20.9	22.7	25.3
7.0	12.6	13.6	14.9	16.5	18.8	20.4	22.0	24.1	27.2
8.0	12.7	13.8	15.2	17.0	19.5	21.3	23.1	25.5	29.1
9.0	12.8	14.0	15.5	17.5	21.2	22.2	24.2	26.8	31.0
10.0	12.8	14.1	15.7	17.8	20.7	22.8	25.0	27.9	32.4
11.0	12.6	13.9	15.4	17.7	20.8	23.0	25.3	28.3	32.9
12.0	12.1	13.4	15.1	17.4	20.4	22.7	25.0	27.9	32.2
13.0	11.5	12.8	14.5	16.8	19.8	22.0	24.2	27.0	31.0
14.0	10.9	12.3	14.0	16.2	19.2	21.3	23.3	25.9	29.5
15.0	10.4	11.8	13.6	15.8	18.7	20.7	22.6	25.0	28.2
16.0	10.1	11.5	13.3	15.5	18.4	20.3	22.1	24.3	27.2
17.0	9.8	11.3	13.1	15.4	18.3	20.1	21.8	23.9	26.5
18.0	9.6	11.2	13.1	15.4	18.3	20.1	21.7	23.6	25.9
Girls									
5.0	13.8	15.0	16.4	18.0	20.1	21.5	22.8	24.3	26.3
6.0	14.4	15.7	17.2	19.1	21.5	23.0	24.5	26.2	28.4
7.0	14.9	16.3	18.1	20.2	22.8	24.5	26.1	28.0	30.5
8.0	15.3	16.9	18.9	21.2	24.1	26.0	27.7	29.7	32.4
9.0	15.7	17.5	19.6	22.1	25.2	27.2	29.0	31.2	33.9
10.0	16.0	17.9	20.1	22.8	26.0	28.2	30.1	32.2	35.0
11.0	16.1	18.1	20.4	23.3	26.6	28.8	30.7	32.8	35.6
12.0	16.1	18.2	20.7	23.5	27.0	29.1	31.0	33.1	35.8
13.0	16.1	18.3	20.8	23.8	27.2	29.4	31.2	33.3	25.9
14.0	16.0	18.3	20.9	24.0	27.5	29.6	31.5	33.6	36.1
15.0	15.7	18.2	21.0	24.1	27.7	29.9	31.7	33.8	36.3
16.0	15.5	18.1	21.0	24.3	27.9	30.1	32.0	34.1	36.5
17.0	15.1	17.9	21.0	24.4	28.2	30.4	32.3	34.4	36.8
18.0	14.7	17.7	21.0	24.6	28.5	30.8	32.7	34.8	37.2

The 2nd, 85th and 95th centiles define the cutoffs for underfat, overfat and obese.

Other assessments have been used to predict disease risk in children and adolescents, such as waist circumference and waist-to-height ratio (waist:height ratio). In recent years, waist circumference has markedly risen among youth (14), and has been seen as a strong risk factor for insulin resistance, high blood pressure, CVD, dyslipidemia and MetS in this population (14,57,59). Thus, increased waist circumference is related with these disorders because it is associated with increased visceral adiposity (VAT) and subcutaneous adipose tissue (SAT). VAT surrounds the internal organs in the abdomen (i.e. liver, kidneys, heart, intestines, etc.), while SAT is located externally to the organs (i.e. around the appendages and over the muscles)

(60). The rate at which free fatty acids (FFAs) are released in the circulation is increased with the greater amount of adipose tissue in men and women (61). VAT is more metabolically adverse than SAT. This is because VAT secretes more proinflammatory cells and disturbs organ function to a greater extent than SAT (60). Thus, both SAT and VAT , but mainly VAT contribute to the delivery of FFAs to the liver, which are then synthesized into TGs and secreted into the circulation as very low density lipoprotein (VLDL) and taken up by other tissues or stored in the liver (62). The increased levels of FFAs in the systemic circulation lead to a variety of metabolic disorders, such as obesity, insulin resistance and hypertension (62).

Studies have shown that increased body mass and central (or abdominal) adiposity is associated with cardiometabolic conditions, such as type 2 diabetes (T2D) and CVD (59,63,64). BMI is used as an assessment of body mass relative to height, and waist circumference or related indexes (such as waist: height or waist:hip ratios) as a surrogate measure of abdominal obesity (63,65). Freedman et al. compared the relationship of BMI-for-age and waist:height ratio to lipids, fasting insulin and blood pressure in 2,498 youths 5-17 years from the Bogalusa Heart Study (63). They concluded that the ability to identify children and adolescents with disease risk factors is similar whether you use BMI-for-age or waist:height ratio (63). Freedman et al. also observed that children with high waist:height ratio had higher levels of LDL-c and TC:HDL-c, and those with a greater BMI-for-age had higher levels of fasting insulin (63), which indicates that these measures are associated with cardiometabolic parameters and disease risk. Therefore, there is consistent evidence that BMI and waist circumference are related to CVD risk factors among children and adolescents (59,63,66,67). However, there are no determined cut-offs for waist circumference to predict health risk in children and adolescents. Sharma et al. proposed a table with

cut-offs for waist circumference and waist:height ratio by age for children and adolescents based on data from the US National Health and Nutrition Survey, cycle III (NHANES III, n=11,930 aged 2-24 years 1988-1994) (Table 3) (66). Other authors also proposed to choose a high waist circumference cut-off, such as 90th - 95th percentile (female > 80cm and male >94cm) (67–69) to signify increased risk, based on waist circumference measures taken from the midpoint between the lowest rib and iliac crest or just above the uppermost lateral borders of the right ilium (68).

Table 3. LMS Parameters for waist circumference and waist:height ratio for 5-19 years children (67).

	Waist circumference						Waist-height					
	Boys			Girls			Boys			Girls		
Age	L	M (cm)	S	L	M	S	L	M	S	L	M	S
5	−2.96	52.3	0.080	−2.52	52.3	0.090	−2.88	0.483	0.078	−2.16	0.486	0.087
6	−3.07	54.2	0.087	−2.53	54.2	0.097	−2.91	0.474	0.084	−2.13	0.477	0.094
7	−3.14	56.1	0.093	−2.53	56.2	0.103	−2.94	0.466	0.091	−2.09	0.470	0.100
8	−3.20	58.1	0.099	−2.51	58.2	0.109	−2.97	0.460	0.096	−2.06	0.464	0.106
9	−3.23	60.0	0.104	−2.48	60.2	0.115	−2.99	0.454	0.101	−2.03	0.459	0.112
10	−3.23	62.0	0.109	−2.44	62.2	0.120	−3.01	0.450	0.106	−2.01	0.456	0.117
11	−3.21	64.0	0.113	−2.40	64.2	0.124	−3.02	0.447	0.110	−2.00	0.454	0.121
12	−3.17	66.0	0.117	−2.35	66.2	0.128	−3.02	0.444	0.114	−2.00	0.453	0.125
13	−3.11	68.0	0.119	−2.29	68.2	0.132	−3.00	0.443	0.116	−2.00	0.454	0.129
14	−3.03	69.9	0.122	−2.22	70.1	0.135	−2.97	0.443	0.118	−2.01	0.455	0.132
15	−2.94	71.9	0.123	−2.15	71.9	0.138	−2.93	0.443	0.120	−2.02	0.457	0.135
16	−2.83	73.8	0.125	−2.07	73.6	0.141	−2.87	0.444	0.121	−2.03	0.460	0.137
17	−2.71	75.6	0.126	−1.98	75.3	0.144	−2.80	0.446	0.122	−2.03	0.464	0.139
18	−2.58	77.5	0.127	−1.87	77.0	0.147	−2.73	0.448	0.122	−2.03	0.468	0.142
19	−2.43	79.3	0.128	−1.76	78.6	0.150	−2.66	0.451	0.123	−2.02	0.472	0.144

More detailed tables with monthly intervals are available in the electronic supplement.
L, skew; M, median; S, coefficient of variation.

2.1.4 Childhood Health Concerns related to Overweight and Obesity

The obesity epidemic has extensive negative implications, especially when the condition is observed at an early age. Childhood obesity can adversely affect almost every organ system and often cause serious consequences (Figure 3), including affecting psychological and physiological health (42,70,71). For example, OB children are up to six times more likely than normal weight children to have

obstructive sleep apnea, which is independently related to the development of behavioural disorders, poor school performance, and poor quality of life later as adults (4).

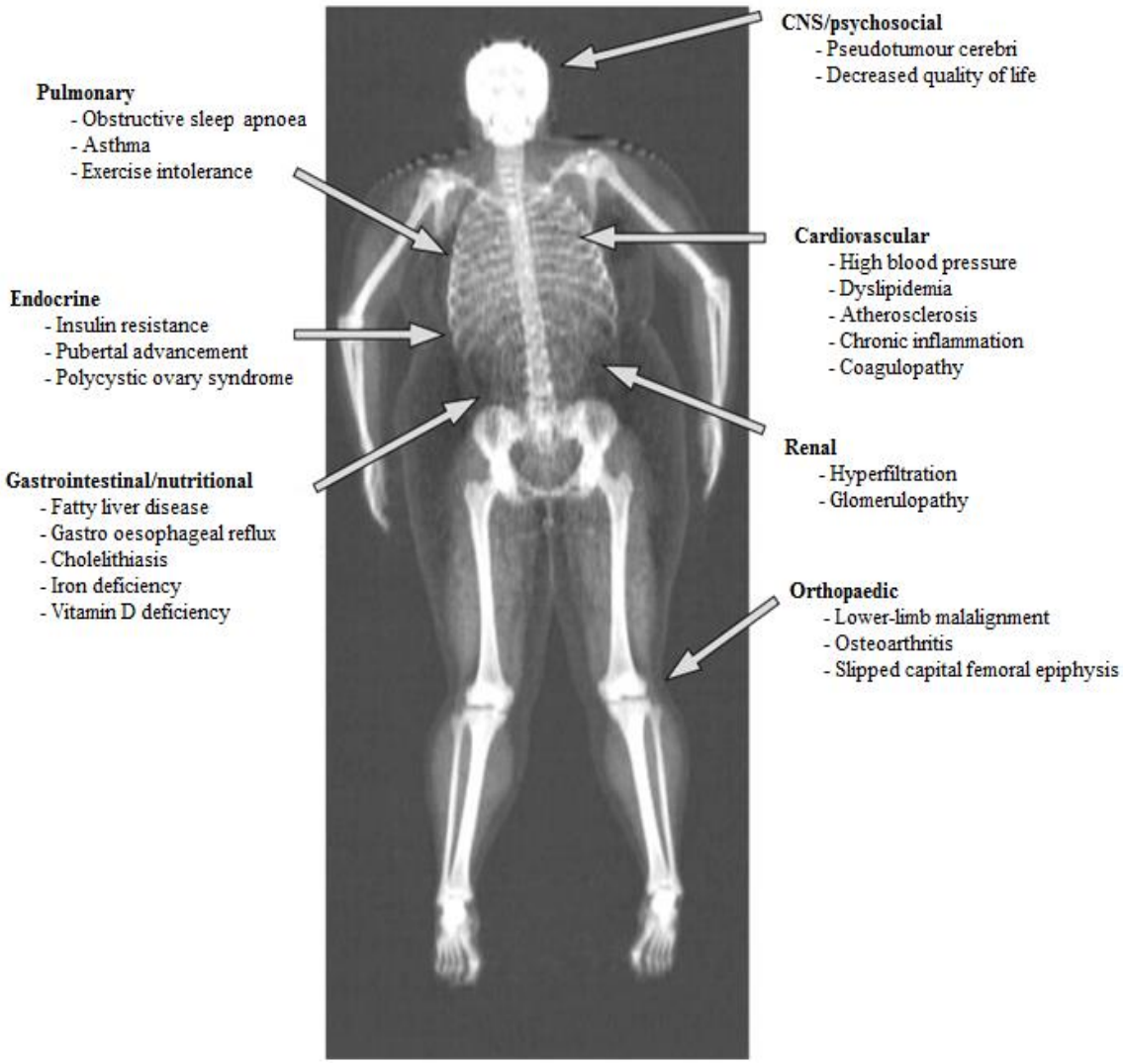

Figure 3. Complications associated with childhood obesity. Image obtained by dual energy x-ray absorptiometry from an obese teenage girl. Adapted from (1)

Many studies have focused on the long-term consequences of being OB from childhood to adulthood (52,72). A study from Bjorge and colleagues has shown that being OW or OB between the ages of 14 to 19 years was associated with increased adult mortality (after age 30) from a wide variety of systemic diseases (73).

Additionally, most pre-adolescent OB children will probably remain OB as an adolescent, and over 70% will remain OB into adulthood (64,74) with a greater prevalence of risk factors for CVD (75).

2.1.5 Factors Leading to Childhood Overweight and Obesity

Youth obesity and its related disorders are a consequence of a chronic imbalance between energy intake and energy expenditure, with social, environmental, genetic and biological factors involved (76). Today's children have a tendency towards sedentary behaviour including excessive television viewing, computer use and video games (which may either reduce energy expenditure, increase energy intake, or both). They also tend to have low physical activity levels; and poorer nutrition, characterized by increased consumption of energy-dense foods including sugar sweetened beverages (SSB), larger portion sizes and eating many meals outside the home (e.g. fast food, take out, etc.) (77).

Other risk factors for childhood obesity are having OB parents (i.e. genetics), and parents not being aware of their children becoming OW (78). A qualitative study in the United States found that obstacles to a healthy lifestyle in a family involve time, practicality, high cost of healthy food, reluctance to modify habits and family preferences for non-healthy foods (79). Sylvetsky and colleagues have found that OW youth believe that obesity is an issue, however they did not link their behaviours to the cause of obesity (80). That is, the children in the study associated being OW with non-modifiable factors like genetics and slow metabolism rather than modifiable factors such as lifestyle (physical activity and diet). Additionally, the youth did not consider lifestyle changes desirable or even achievable. The study suggested that

education of healthy habits would be beneficial to children so their desirability and knowledge for healthy foods/choices would increase (80).

Canadian epidemiological evidence shows that physical activity among children aged 7 to 11 is negatively associated with OW and obesity, while TV viewing and video game playing increase the risk of excess weight gain (81). Therefore, chronic exposure to these obesogenic factors may stimulate weight gain over the years (5). Modifying these behaviours should be regarded as a high priority for interventions aimed at the prevention of childhood obesity (80).

2.2 LIFESTYLE MODIFICATION DURING CHILDHOOD

High levels of inactivity (e.g. tv watching, using computers, playing video games), low levels of physical activity and inappropriate diet are typical in children's routines today (82), and these behaviours may be established at an early age (41). Introduction of habitual healthy behaviours that can be adopted by the young population can have a significant effect in correcting the early stages of metabolic abnormalities. This will contribute to reducing obesity and related comorbidities (83). For that reason, the promotion of lifestyle change should be implemented among all pediatric populations, not just for those currently defined as OW/OB, as it will help build a strong foundation of childhood healthy living that can be carried on into adulthood (84).

It is widely accepted that treating childhood OW/OB is an important step in responding to the obesity epidemic (85). Management interventions involving family support, behaviour modifications, and lifestyle changes are difficult to put into practice, and in some cases, may require the input of multidisciplinary professional

teams (86,87). As a matter of fact, lifestyle changes require a high level of motivation and active involvement from the children/adolescents and their families to achieve positive outcomes, such as fat loss and improved metabolic health (76). Weight-management programs for youth, including isolated programs (diet or physical activity or behaviour) and combined programs (combination of exercise, diet, and/or behavioural modification) have been investigated. A systematic review in OW/OB participants ≤18 years reported that lifestyle interventions (diet plus exercise) were more effective in improving risk factors, such as HDL-c, fasting glucose and insulin, in interventions that lasted over 6 months, than in programs with diet only and/or exercise only interventions (88), which highlights the need to promote healthy eating coupled with frequent physical activity to improve the overall health of OW/OB children. Similarly, a Cochrane systematic review suggested that the best approach to reduce FM of OB children and improve metabolic markers is to implement a lifestyle modification, family-based intervention, focused on combining changes in behaviour, dietary and physical activity patterns for the children and their families (89). Therefore, combined programs tend to be more effective in children and adolescents for obesity management because the beneficial changes are usually kept for a longer period, since their lifestyle was modified and likely implemented for the entire family, and they were educated about a healthy living (88). For OW children and adolescents, the goal is to reduce the rate of fat gain while achieving normal growth and development (90).

2.2.1 The Role of Physical Activity and Health in Overweight/Obese Children

2.2.1.1. Physical Activity Guidelines

In order to encourage children and adolescents (5-17 years) to achieve high levels of physical activity the Canadian Society of Exercise and Physiology (CSEP) has developed the Canadian 24-hour Movement Guidelines for Children and Youth (91). According to the guidelines, children and adolescents should accumulate at least 60 min/day of moderate to vigorous exercise combined with several hours of a variety of structured and unstructured light physical activities, sufficient hours of sleep (9-11h/night for 5-13 year olds and 8-10h/night for 14-17 year olds), and low levels of sedentary behaviour daily (no more than 2 h/day of screen time and limited sitting for long hours) (91). Despite the promotion of the physical activity guidelines, most Canadian school-aged children and youth (5 to 17 years) do not achieve the minimum recommendation of physical activity, with only 13% of boys and 6% of girls getting an average of at least 60 minutes of moderate-to-vigorous daily physical activity as recommended. Thus, our pediatric population spends the majority of their time being inactive (92).

2.2.1.2. Physical Activity and Health

Regular participation in different types of physical activity is essential for healthy growth and development (93). Evidence shows that physical activity can improve body composition, cardiometabolic parameters, aerobic fitness, muscular strength, movement skills, and bone health in children (94,95). Regular physical activity can also improve academic performance and promote feelings of well-being (96). The positive lifestyle behaviours such as participating in daily physical activity

that begin during childhood and adolescence tend to carry over into adulthood (97). Thus, daily participation in fitness activities, recreational sports and outdoor games would help to improve the well-being and health of children and adolescents (97).

Regular physical activity increases energy expenditure and metabolic rate at rest; decreases fat storage; increases tolerance to glucose and improves insulin sensitivity; and decreases inflammatory state in children and adolescents (97–99). There is an inverse relationship between physical activity levels and the development of obesity in children (98,100–102). In this sense, increasing physical activity during childhood may be protective against future weight gain and metabolic diseases (10).

2.2.2 The Role of Diet in Health

Childhood and adolescence is an important period for growth and development (103). However, a poorer diet leading to an insufficient intake of essential nutrients, higher levels of inactivity leading to body fat accumulation leads the pediatric population towards a state of poorer metabolic health (104). Most cardiometabolic risk factors are potentially reversible with lifestyle change during childhood (105).

2.2.2.1. Dietary Guidelines

Canada's Food Guide recommendations of servings per day in the 4 food groups for children and adolescents is shown in Table 4 (13). The Canadian Community Health Survey, Cycle 2.2 Nutrition (CCHS 2.2), conducted in 2004, indicated that 7 out of 10 children age 4-8 years had less than 5 svgs/d of vegetables and fruits.

Table 4. Canada's Food Guide recommendations for children and teenagers in servings per day. Retrieved from (13).

	Children			Teens	
Gender	Girls and Boys			Females	Males
Age in Years	2-3	4-8	9-13	14-18	
Vegetables and Fruit	4	5	6	7	8
Grain Products	3	4	6	6	7
Milk and Alternatives	2	2	3-4	3-4	3-4
Meat and Alternatives	1	1	1-2	2	3

At age 9-13 years, 68% of boys and 62% of girls did not meet the minimum intake of vegetables and fruits. Regarding the dairy food group, 61% of boys and 83% of girls age 10 to 16 years did not meet their recommended minimum of 3 svgs/d. Additionally, more than a quarter of children age 4-8 years did not meet the recommendations for grains, with the same pattern for meat and alternatives (13). The survey indicated that Canadian children are not consuming enough nutrients for their development and growth. This is also shown in another part of the survey, where it indicates that Canadian youth have inadequate intakes of fibre; vitamin A; vitamin D; magnesium; phosphorus; potassium and calcium (106). A lot of these nutrients are directly related to bone health, and are required during adolescence when bone mineral accrual rate is the highest (107). In 2010, the Institute of Medicine Dietary Reference Intake committee set the Recommended Dietary Allowances at 1,300 mg/day of calcium and 600 IU/day of vitamin D for children ages 9–18 years in an effort to achieve greater amounts of nutrients essential for bone health; while Canada's Food Guide recommends 3 to 4 servings of dairy/day (13). However, as shown above, a high percentage of Canadian youth do not achieve the minimal recommended consumption of these nutrients necessary for optimal health (108). In fact, children and adolescents are eating more empty calorie foods (energy-dense,

nutrient-poor foods), which contributes to this populations' risk of OW/OB and poor metabolic health.

The CCHS 2.2 survey showed that children and adolescents aged 4 to 18 years had 31% of their daily calories derived from the "other foods group", which includes: sugar, jam, honey, candies; chips (potato, corn, etc.); butter, cooking oils and salad dressings; soft-drinks, tea and coffee; and condiments such as ketchup, mustard and pickles (13). This greatly affects the overall quality of their diets. This survey shows that youth are choosing energy-dense/nutrient-poor foods instead of nutrient-dense foods daily. Children/adolescents and their parents should be aware of the health consequences of eating poor quality food that include low levels of important nutrients, as these dietary practices can lead to serious health problems (e.g., T2D, hypertension, and MetS) in childhood and eventually in adulthood (109).

2.2.2.2. Lifestyle Intervention

Lifestyle interventions for obesity treatment in children and adolescents have presented improvements in body composition, anthropometrics, cardiorespiratory fitness, muscle strength and/or cardiovascular risk factors (e.g. dyslipidemia and insulin resistance) (5,9–11,110). Bianchini et al. examined the effects of a 16-week, multidisciplinary intervention based on cognitive behavioural therapy on 86 OB adolescents (10-18 years). The participants were divided into a control group (maintained the routine) and an intervention group, which had weekly meetings and lectures with a psychologist, nutritionist, exercise professional and pediatrician. After 16 weeks, the intervention group showed improved waist circumference, TC, blood pressure and a reduced number of risk factors for MetS compared to the control group (110). This study indicates that behavioural therapy including a multidisciplinary

approach (psychological, nutritional and physical activity) can improve metabolic profiles in OB adolescents.

Dietary modification, such as decreasing the consumption of certain types of fats and simple sugars, and increasing consumption of omega-3 fats (e.g. fish oil, flaxseed oil), helps to decrease TGs levels, decrease weight gain and improve blood lipids (111). An intervention with 42 boys and 43 girls, aged 6 to 15 years, evaluated the effects of a eucaloric diet (not intended for weight loss and appropriate for the children's height, body mass and age) and physical activity on metabolic parameters and BMI during a 1-year nutritional-behavioral intervention in OB children (5). The intervention was to consume a eucaloric diet consisting of 12-15% protein, 55-60% carbohydrates, 25-30% fat, and perform a minimum of 60 minutes of moderate-to-vigorous-intensity physical activity daily tailored to individual preferences. The participants and their parents received nutritional, exercise and behavioral advice at baseline with written educational materials. At the end of the study, children showed increased HDL-c ($p=0.034$), decreased TGs ($p=0.024$) and a decreased TGs:HDL-c ($p = 0.018$). BMI percentile was lower post-study than at baseline ($p <0.0001$), and so was triceps skinfold thickness ($p <0.038$). No difference was found for waist circumference ($p = 0.150$). Prevalence of MetS was reduced by 71.4% and prevalence of insulin resistance decreased by 30%. This study showed that longer term interventions where youth participants consume a eucaloric diet with healthy foods (i.e. with no energy restriction), and perform physical activity can result in improvements of blood lipids markers, insulin sensitivity and a reduction of BMI thus achieving a greater metabolic health profile (5). A multi-cohort study used data from the 'Project HeartBeat!' of children and adolescents in the United States to assess multiple profiles for lipids, anthropometrics and blood pressure to identify high risk

groups of children and youth for CVD (72). The cohort analysis showed that high risk groups had greater BMI, percent body fat, waist circumference as well as higher TGs and LDL-c, and lower HDL-c. Thus, these findings help prove the effectiveness of measuring these variables in order to implement early interventions for decreasing or delaying unfavorable metabolic changes and improving cardiovascular outcomes (112). Another study with similar findings was 'The Princeton Lipid Research Clinics Follow-up Study', where participants were followed for 25 years (72). Between 6-19 years old, 4% of 771 youth had pediatric MetS. Of these 4% with pediatric MetS, 68% continued to have MetS as adults and 19.4% had CVD as adults (72). Hence, treating and preventing MetS risk factors during childhood could prevent future CVD, making targeted interventions in youth even more important.

The success of obesity treatment should be measured according to health benefits and well-being, instead of just the amount of body mass/fat lost, according to the Canadian Obesity Network (113). For this reason, studies in a youth population should focus on improving metabolic health and facilitating lifestyle change through healthy dietary intakes, improvement of fitness and strength, and implementation of daily physical activity, along with family-based support.

2.2.3 RCTs using Diet and Exercise to Improve Metabolic Variables

A systematic review by Ho and colleagues presented several meta-analyses of RCTs involving the effects of lifestyle interventions (diet, exercise, and/or behavioural change) on cardiometabolic outcomes in OW children (88). The details are listed below in Table 5. One meta-analysis of 5 studies including 440 OW and OB participants, age 8 to 16 years old showed that lifestyle intervention improved TC

compared to no treatment in the short-term (-0.40mmol/L, 95%CI: -0.51 to -0.30; length: 4 to 6 months) and long-term (-0.24mmol/L, 95%CI: -0.30 to -0.17; length: 1 to 2 years) (88). The TGs levels for the same 5 studies also improved with lifestyle intervention (short term: -0.20mmol/L, 95%CI: -0.35 to -0.05; and long term: -0.09mmol/L, 95%CI: -0.11 to -0.07). Another meta-analysis of 4 studies including 372 participants during a period of 4 to 12 months showed improvements in LDL-c levels (-0.30mmol/L, 95%CI: -0.45 to -0.15) with a lifestyle intervention. But, no differences were found for HDL-c levels ($p = 0.22$) (88).

Another intervention study by Saavedra et al. determined the effects of diet and/or exercise on body composition and metabolic parameters of OB children (8-11 years) during 6 months (10). The 42 participants (27 boys, 15 girls) were divided into three groups, exercise only (3x90min/week), low calorie diet only (~1500kcal/d, 57% carbohydrates, 17% proteins and 26% fats), and exercise+diet group. With respect to the metabolic markers, while the exercise group presented no change in any parameter (possibly because the participants maintained their poor eating habits), the diet group presented reduced levels of TGs ($p=0.046$), glucose ($p=0.007$) and HOMA-IR ($p<0.001$), while the exercise+diet group showed improvements in HDL-c ($p=0.038$), LDL-c ($p=0.050$), LDL-c:HDL-c ($p=0.009$) and TC:HDL-c ($p=0.004$). For the body composition parameters, there were no significant changes for the diet group, in the exercise group there were reductions in FM ($p<0.001$), and in the exercise+diet group there were reductions in body mass ($p=0.024$), FM ($p=0.002$), waist circumference ($p<0.001$) and hip circumference ($p<0.001$). Overall, the results from the combined intervention presented more positive changes than exercise alone or diet alone when comparing the metabolic and body composition results. Also, there were no

significant differences between the diet and exercise alone groups, highlighting the need to combine the two to improve overall health of OB children (10,88).

Evidence has shown that the main approach to decreasing MetS and related disorders is to implement a lifestyle change in children and adolescents' routine to suppress the gain of body fat. This population needs to increase physical activity and improve their eating habits (114). The Obeldicks study examined the implementation of lifestyle interventions to modify MetS risk factors in OB children (2). It was a 1-year outpatient program involving nutritional education, physical activity and behaviour therapy. The study had 288 OB children aged 10-16 years being part of the intervention arm, and 186 participants in the control group. The lifestyle intervention group improved waist circumference, LDL-c and blood pressure, while TGs, HDL-c and fasting glucose did not change significantly. In addition, the decrease in prevalence of MetS was associated with the reduction in body mass in the majority of OB participants (2). Therefore, this study reaffirms the importance of long-term multidisciplinary lifestyle change for OB children, as MetS and its components significantly decrease with physical activity and healthy eating.

Likewise, even a short-term intensive intervention by Luo et al. resulted in significant changes in MetS risk factors in 167 OB Chinese children aged 11 to 13 years (9). They analyzed body composition and anthropometrics, blood pressure, and fasting blood samples for insulin, glucose, TC, TGs, LDL-c and HDL-c. In addition, ten children in the intervention arm were diagnosed with MetS, and all participants had at least one MetS risk factor before commencing the study. After 6 weeks of high volume aerobic exercise (6 days/week, twice daily, for 3h each session) and a controlled calorie diet (1600-2000 kcal/day based on each participant basal metabolic rate), they found significant decreases in TGs, LDL-c, TC and fasting insulin (p

<0.05) in boys and girls, except for fasting blood glucose in boys (p=0.09), compared to controls. After the trial, none of the children were diagnosed with MetS in the intervention group (9).

Table 5. RCTs using lifestyle modification with lipid and glucose homeostasis outcomes.

Citation & Participants	Intervention	Results
Verduci et al. 2015 (5) Italy 42 boys and 43 girls (n=85) OB 6-15 years	1-year (1 group) Normocaloric diet and physical activity for all participants	↔ fasting insulin, glucose & HOMA-IR ↔ TC, LDL-c ↓TGs ↓TGs:HDL-c ratio ↑HDL-c ↓ BMI ↔ waist circumference
Ho et al 2013 – Systematic Review, meta-analysis (3) Australia N=519 OW/OB 5-18 years	3 to 6-months intervention (2 groups) Exercise+Diet *vs* Diet **Dietary interventions:** calorie restriction approach, Traffic Light*, general dietary advice. **Exercise interventions:** aerobic exercise, resistant training and combination of aerobic plus resistant training.	↓TGs ⇒ D > E+D ↑HDL-c ⇒ E+D > D ↓ LDL-c ⇒ D = E+D ↓ Fasting Insulin ⇒ E+D > D ↓ Fasting Glucose ⇒ E+D > D
Ho et al 2012 – Systematic Review, meta-analysis (88) Australia N=372 OW/OB 8-16 years	4 to 12-month intervention (2 groups) Exercise+Diet *vs* Control **Dietary intervention:** Traffic Light*, hypocaloric or a calorie restriction approach. **Exercise intervention:** Supervised physical activity sessions or exercise training	↓ LDL-c ↔ HDL-c ↔ Fasting Glucose ↓ Fasting Insulin (over 12 months) ↓ HOMA-IR (over 12 months)
Saavedra et al. 2011 (10) Spain	6-months intervention (3 groups) Exercise *vs* Diet *vs* Exercise+Diet	E = ↔ metabolic markers ↓ BMI, ↓ body fat D = ↓glucose

27 boys and 15 girls (n=42) OB 8-11 years	**Exercise**: 3x/w 90min exercise (n=11) **Diet:** low calorie diet (n=16) **Exercise+Diet**: 3x/w 90min exercise + low calorie diet (n=15)	↓HOMA-IR ↓TGs ↔ body composition E+D = ↑HDL-c ↓LDL-c ↓ BMI ↓ Body fat and weight ↓ Waist circumference
Reinehr et al 2009 (2) 'Obeldicks' Study Germany N= 474 (boys and girls) OB 10-16 years	1-year intervention (2 groups) Exercise+Diet *vs* Control **Exercise+Diet**: 1x/w of exercises + nutritional course + behaviour therapy (n=288) **Control:** maintained regular activities (n=186)	E+D = ↔ Fasting Glucose ↓2h glucose in oGTT ↓ LDL-c ↔ HDL-c ↔ TGs ↓ BMI ↓ Waist Circumference C = ↔ metabolic markers ↑ BMI ↑ waist circumference
Luo et al. 2013 (9) China 77 girls and 90 boys (n=167) OB 11-13 years	6-weeks intervention (2 groups) Exercise+Diet *vs* Control **Exercise+Diet:** 2x/d 3h exercise (6x/w) + low calories diet (n=95) **Control:** maintained regular activities (n=72)	E+D = ↓ Fasting insulin both genders ↓ Fasting glucose only in girls ↓HOMA-IR both genders ↓TC both genders ↓LDL-c both genders ↓TGs both genders ↑HDL-c both genders ↓ BMI ↓ Body fat and weight ↓Waist Circumference C = ↑ fasting insulin and HOMA-IR ↔ fasting glucose ↑ TC, LDL-c and TGs ↑ body mass/fat
Chen et al. 2005 (11) USA 10 boys and 6 girls (n=16) OW 10-17 years	2-weeks residential program (1 group) Food provided at ad libitum with high-fiber and low-fat diet and daily aerobic exercises of ~ 2h30 for all participants (n=16)	↓ Fasting insulin ↓ HOMA-IR ↓TC ↓LDL ↓TGs ↔ HDL-c ↓ BMI ↓ Body mass/fat

OW = overweight, OB = obese, TC = Total Cholesterol, HDL-c = High Density Lipoprotein Cholesterol, LDL-c = Low Density Lipoprotein Cholesterol, TGs = triglycerides, HOMA-IR = Homeostatic Model Assessment Insulin Resistance, E =

Exercise Group Intervention, D = Diet Group Intervention, D+E = Diet and Exercise Group Intervention, C = Control Group Intervention * Traffic Light diet is a calorie-controlled approach in which foods in each category are colour-coded according to their calorie density per average serving: green for low-calorie foods that can be eaten freely; yellow for moderate-calorie foods that can be eaten occasionally; and red for high-calorie foods that should be eaten rarely.

2.3 DAIRY

2.3.1 Dairy Consumption and Nutrient Intake in Childhood

Milk and other dairy foods are great sources of macronutrients and micronutrients that are important in children's diets. Dairy in the diet plays a role in meeting numerous nutrient intake recommendations affecting several facets of growth and development (12). Dairy macronutrients include: carbohydrates (lactose and other sugars); Fat (saturated and unsaturated fat including essential [alpha linolenic acid and linoleic acid] and non-essential fatty acids [butyric acid and palmitoleic acid]); and high-quality protein (whey, casein and other peptides and bioactive factors that have specific effects on growth). Milk also contains micronutrients such as phosphorus, magnesium, zinc, potassium, vitamin A, calcium and vitamin D, which are essential for children's growth (12,115). Fulgoni *et al.* suggested that the micronutrients found in a serving of dairy are difficult to replace with other foods in the American diet (116).

Calcium benefits the growth and maintenance of healthy bones and teeth, as well as aiding in the regulation of blood pressure, muscle contraction and blood clotting (115). Dairy calcium is highly bioavailable and can account for more than 50% of children's total calcium intake per day. A longitudinal study by Moore et al. collected data in children in the United States and showed that consuming at least two cups of milk (473 mL) per day was associated with significantly higher mean calcium

intake ($p < 0.0001$) compared to children who did not consume milk regularly (117). However, calcium intakes among children and adolescents generally falls below recommendations because they do not consume adequate amounts of dairy or calcium-fortified foods (13). Another essential nutrient that is fortified in some dairy products is vitamin D, which is responsible for several functions in the body, and has a direct relationship with calcium balance (118). A systematic review in youth showed that dairy consumption was positively associated with improvements of bone structure (119). Milk only has traces of natural vitamin D, for that reason milk is fortified in some countries (108,120). In Canada, vitamin D is added to milk with 35-40 IU/100g by law (121).

Volek et al. investigated the effects of increased milk intake and resistance training on body composition and bone mineral density in 28 healthy boys (13-17 years) for 12 weeks (33). The adolescents were divided into 2 groups, one group consumed 3 servings of 1% milk (708 mL) (n=14) and the other consumed unfortified apple or grape juice (n=14). Participants from both groups exercised for 1h 3 days/week for 12 weeks, milk and juice were provided on these days and participants were instructed to maintain their usual diet. Significant changes in body composition, bone and maximal strength was observed after the 12-week intervention in both groups. The only variable that significantly differed between the milk and juice groups was whole-body bone mineral density, which increased to a greater extent in the milk group. Therefore, this study indicates that the increased intake of milk (including calcium and vitamin D) may lead to improvements in whole-body bone mineral density, optimizing bone development in adolescent boys. Additionally, the milk group presented with higher intakes of protein, vitamins A, D and B_2, calcium, magnesium, and phosphorus, indicating a higher intake of nutrients compared to the

juice group (33). Similar results were seen in a study by Stear et al., who investigated the effects of calcium supplementation and exercise intervention on the bone mineral status of 144 adolescent girls (16-18 years) for 15.5 months (34).

2.3.2 Milk and Sugar-Sweetened Beverage Consumption

Milk is a great source of essential nutrients for adolescents, who experience dynamic growth changes and puberty (122). Several studies have demonstrated that when milk is excluded from adolescent diets, it is difficult for them to achieve the daily requirements for calcium and other essential nutrients (123,124). For this reason, consumption of the recommended amounts of dairy foods may help adolescents meet their nutritional requirements and improve their diet quality (122).

A recent review by Dror and Allen showed that the consumption of milk declines as children get older (125). Other authors indicated that males consume more dairy than females (126–129), possibly influenced by the misperception that dairy foods are fattening (130). The frequency of dieting by adolescent girls has been associated with insufficient intakes of milk and related foods possibly due to the restriction of calories and fat to lose weight (126,131). In addition, the decrease of milk consumption has been correlated to the increase of sugar-sweetened beverage (SSB) and fruit juice intake (132–136). Thus, the concomitant increase in childhood obesity and decrease in dairy intake have led researchers to hypothesize that the two may be related (137). Indeed, SSB consumption has been positively associated with increased body mass and risk of obesity (138), and negatively associated with micronutrient intake (139) in children and adolescents. According to Forshee and colleagues, US adolescents drink more SSB per day than milk (140). Adolescent

males drink an average of 22 ounces (650mL)/day of SSB; more than twice their intake of fluid milk (10 ounces), and females drink an average of 14 ounces/day of SSB and only 6 ounces/day of fluid milk (140). Another study demonstrated that a small sample of children (aged 6 to 13) at a 4- to 8-week summer day camp were offered both milk and fruit-flavored SSB. Children and adolescents chose SSB instead of healthier choices, like milk, even when both options were available for them (136).

According to data from the Continuing Survey of Food Intake by Individuals (CSFII) in the United States, for each 30mL decrease in milk intake by children and adolescents (aged 5-18 years), there is an increase of approximately 126mL in SSB intake. This corresponds to an increase of 31 kcal and a reduction of 34 mg of calcium, for every 30mL of milk substituted (132). While milk is a nutrient-dense beverage that is directly related to increased energy intake, when removed from the diet it is usually substituted by other energy-dense foods and beverages that are not nutrient-dense (141,142). This has been said to partly explain the increases in childhood obesity. To improve the health of our youth, the consumption of SSB should be drastically reduced, in addition to promoting nutritional education to encourage youth (and their parents) to change their dietary habits. Children, adolescents and their parents should be aware of the health consequences of energy dense nutrient poor foods that include low levels of important nutrients, as these dietary practices can lead to serious health problems (e.g., T2D, hypertension, and MetS) in childhood and eventually in adulthood (109).

2.3.3 Dairy consumption and Cardiometabolic Variables

Several observational studies have indicated that the consumption of dairy

products was inversely associated with CVD risk factors in children and adolescents (Table 6) (16–21). In adults, intervention studies have suggested that increased intake of dairy was inversely associated with incidence of diabetes, hypertension, poor cardiovascular health, MetS and increased inflammation (119,143–145). However, a recent comprehensive review by Drouin-Chartier et al. did not confirm these same findings, showing a null association, although not deleterious, between dairy and cardiometabolic health in adults (146). The authors examined the impacts of dairy foods and dairy fat on cardiometabolic risk in adults based on data from RCTs (146). This review suggested that total dairy consumption, irrespective of fat content, has no detrimental impact on a large array of cardiometabolic variables, including lipid-related cardiometabolic disease disk factors, low-grade systemic inflammation, blood pressure and vascular function. Same trend is observed for glucose and insulin resistance in the short-term, but may be beneficial in the long-term (146). Thus, this comprehensive review indicates that dairy intake has no risk of potential harmful effects on cardiometabolic health of adults.

Abreu et al. examined the association between milk consumption, exercise and abdominal obesity in 1,209 adolescents aged 15-18 years in a cross-sectional study (14). The study shows that the group of adolescents with higher milk intake (≥2 svgs/d) who were active had a lower proportion of abdominal obesity than the other groups analyzed. Thus, this cross-sectional study suggests that higher milk intakes may contribute to the reduction of abdominal obesity in youth, possibly due to the beneficial effects of calcium on weight and body fat loss (23–25). Dairy consumption has been associated with lower insulin resistance in two cross-sectional studies, Hirschler et al. (19) and Zhu et al. (17). The former examined the effects of milk intake on insulin resistance and components of MetS in 365 school children (5-14

years) in Buenos Aires. Children were divided into 3 categories of frequency of whole milk consumption per day, group I (≤1 glass, n=143), group II (2-3 glasses, n=197) and group III (≥4 glasses, n=24). They found that a higher intake of milk was associated with a healthier lifestyle, and increased consumption of milk was inversely correlated with HOMA-IR, but no significant associations were found among the groups for HDL-c, TGs and BMI. The authors performed a linear multiple regression analysis to investigate whether the association between milk consumption and insulin resistance was due to milk or other aspects of a healthy diet, such as fruits and vegetables intake. They found that milk consumption was inversely and significantly associated with HOMA-IR ($\beta = -0.28$; $p = 0.026$), but fruit and vegetable consumption was not significantly associated ($\beta = 0.008$; $p = 0.903$) (19). Therefore, increased milk consumption was associated with a greater insulin sensitivity. Zhu et al, had similar findings to Hirschler et al., where higher yogurt intake was correlated with lower insulin resistance (HOMA-IR), but not with blood lipids, fasting glucose or body composition (17).

Bel-Serrat et al., in another cross-sectional study with adolescents from 8 European cities (HELENA study), investigated the food groups that best discriminate adolescents as high and low CVD risk, and the relationship between dairy consumption and these risk factors (16). The study found an inverse relationship between milk consumption and TGs (-0.17, $p = 0.02$), and milk consumption and CVD risk score (-0.14, $p = 0.04$) in girls. Yogurt and milk- and yogurt-based beverages consumption was negatively associated with waist circumference in boys and girls (-0.17, $p = 0.04$; -0.21, $p = 0.004$, boys and girls respectively), and a positive correlation with cardiorespiratory fitness (0.15, $p = 0.03$; 0.18, $p = 0.01$, boys and girls respectively).

Kelishadi et al. conducted a RCT to determine the long-term effects of a dairy-rich diet on abdominal obesity and MetS risk factors in 120 OB pre-pubertal children (21). All participants attended 6 consecutive monthly family-centered education sessions about healthy lifestyle (increasing physical activity and healthy nutrition) that were conducted by a nutritionist and pediatrician. The participants were randomly assigned to 3 groups: a dairy-rich diet (>800 mg calcium/d), a calorie-restricted diet (-500 kcal/d); and a control group that received no dietary recommendation other than what was discussed in the healthy lifestyle education sessions. The 3 groups were then followed-up twice a year for 3 years (for a total of 36 months). In all groups, TGs, fasting insulin, HDL-c and HOMA-IR improved after the 6-month trial without a significant difference between groups. During the follow-up (remaining 30 months), TGs, fasting insulin and HOMA-IR had risen, and HDL-c had fallen in all 3 groups, but in the dairy-rich group, these markers were significantly better compared to the other groups. BMI percentile and waist circumference significantly decreased after the 6-month trial in all groups. During the follow-up period, there was a sustained rise in BMI and waist circumference until the end of the study, however it was significantly lower in the dairy-rich group compared to the other groups. The study suggested that in addition to lifestyle changes and improvement of physical activity and dietary habits, a diet rich in dairy products with no change in energy or macronutrient intake may be an acceptable regimen, and can be a safe and practical strategy for weight management in this population. It may also be a way to improve insulin resistance and other components of the MetS (TGs and HDL-c) in OW children without the restriction of calories (21).

There is a lack of consistent evidence for the effects of dairy consumption on cardiometabolic markers in children and adolescents. Therefore, this thesis may start

to answer a few questions regarding the effects of dairy consumption, combined with healthy eating and regular exercise on metabolic health of OW and OB adolescent girls.

Table 6. Studies examining Dairy consumption and Cardiometabolic Health in Children and Adolescents. Note: Kelishadi et al., (2009) is the only RCT.

Citation & Participants	Study Design	Results
Bel-Serrat et al. 2013 (16) Data from HELENA Study (2006-2007) N=3,528 (~50% males) 12.5 – 17.5 years	Cross-sectional 24-hour recall at 2 time points of study	↑ Milk, Yogurt, milk- and yogurt-based beverages ***Associated with*** ↓ TGs (only in girls) ↓ CVD risk score (only in girls) ↑ Cardiorespiratory Fitness (both genders) ↓ waist circumference (both genders) ↓ Body fat/weight (both genders)
Zhu et al. 2015 (17) Data from NHANES (2003-2006) N=5,124 (2,498 males) 2 – 18 years	Cross-sectional 24-hour recall and FFQ	↑ Yogurt intake ***Associated with*** ↓ fasting insulin, HOMA-IR and ↑ QUICKI ↔ fasting glucose, lipids, blood pressure or body composition
Abreu et al. 2014 (18) Data from a longitudinal school-based study (n=1,515) (2008) N=494 (208 males) OW/OB 15 – 18 years	Cross-sectional FFQ	↑ Milk intake only ***Associated with*** ↓ CVD risk score yogurt, cheese and total dairy ***Associated with*** ↔ CVD risk score
Hirschler et al. 2009 (19) N=365 (175 males) normal weight/OW/OB 5 – 14 years	Cross-sectional Mothers completed questionnaires about their children's lifestyle	↑ Dairy intake ***Associated with*** ↓ HOMA-IR ↓ Waist circumference ↔ HDL, TGs, BMI

Kelishadi et al 2008 (20) Data from CASPIAN Study (2003-2004) N=4,811 (2,248 males) 6 – 18 years	Cross-sectional FFQ	↑ Dairy intake + fruits & vegetables ***Associated with*** ↓ MetS and CVD in children/adolescents of both genders
Kelishadi et al. 2009 (21) N=120 obese children 5 – 6 years	Randomized Controlled Trial 3-day dietary record was filled in by the parents 36 months (6-months active intervention) 6 consecutive monthly sessions about healthy lifestyle education and 30-months follow-up for all 3 groups 1) Dairy rich diet (>800mg calcium/d) with no change in macronutrient intake 2) Calorie restriction diet (-500kcal) with dairy intake recommended 3) Control group (no dietary recommendation other than the healthy lifestyle education)	After 6 months of education sessions, all groups: ↑ HDL ↓ TGs ↓ Fasting insulin ↓ Waist circumference During follow-up waist circumference, TGs, insulin and HOMA-IR increased and HDL decreased in all 3 groups. But in the dairy-rich group these markers were significantly better compared to the other groups, as well as waist circumference.

FFQ = Food Frequency Questionnaire; **OW/OB** = Overweight/Obese; **NHANES** = Third National Health and Nutrition Examination Survey; **CVD** = cardiovascular disease; **CVD risk score** = a continuous risk score was computed using total cholesterol/high density lipoprotein-cholesterol ratio, triglycerides, homeostatic model assessment insulin resistance (**HOMA-IR**), systolic blood pressure, percentage body fat, and cardiorespiratory fitness. For each variable, age- and sex-adjusted z scores were computed. The CVD risk score was constructed by summing the z scores of all risk factors; **MetS** = metabolic syndrome.

2.3.4 Mechanisms of Dairy consumption effects on Cardiometabolic Variables

Milk components have been studied for their effects on cardiometabolic health and adiposity, especially calcium. It has been proposed that calcium increases fecal

lipid excretion (137), thermogenesis and lipid oxidation (23–27). In addition, it has been proposed that dairy bioactive peptides and fatty acids have impacts on body mass/fat and the metabolic profile (29,30). Thus, most of their effects on the cardiometabolic variables are indirect, and are mediated through body mass/composition change.

2.3.4.1 Calcium

The plausible mechanism most frequently cited for the effect of dietary calcium on the regulation of adipose tissue mass is its direct action on parathyroid hormone (PTH) and 1,25$(OH)_2$D (calcitriol); the active metabolite of vitamin D. Low serum calcium (due to a reduced dietary calcium intake) activates PTH release from the parathyroid gland. PTH stimulates renal hydroxylation of 25(OH)D to 1,25$(OH)_2$D. Then, 1,25$(OH)_2$D directly affects the adipocyte by allowing calcium channels to open, increasing intracellular calcium levels. The increase of intracellular calcium promotes the activation of the enzyme responsible for intracellular lipogenesis; fatty acid synthase (FAS). FAS also inhibits lipolysis (breakdown of fat), which stimulates TGs storage. Thus, suppression of calcitriol and PTH levels via increased dietary calcium may be one potential mechanism to prevent and manage obesity, as it will diminish the stimulation of *de novo* lipogenesis (23–27). This mechanism is illustrated in Figure 4.

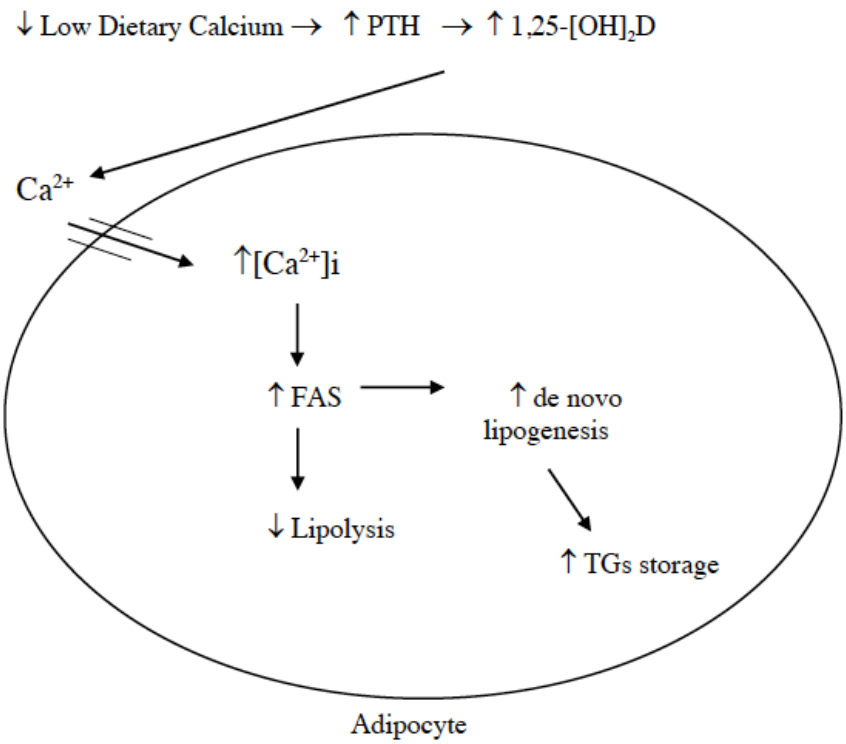

Figure 4. The effect of low dietary calcium on the modulation of adiposity. Adapted from (136).

Evidence also suggests that calcium reduces fat absorption from the gastrointestinal tract (28,147,148). This mechanism is associated with the capability of calcium to increase fecal fat excretion via the production of insoluble calcium-fatty acid soaps in the gut, and by binding to bile acids, which weakens the formation of micelles. Consequently, there is an increased level of fecal fat elimination. No studies have specifically examined these mechanisms in children and adolescents. It is possible that the dynamic metabolic changes occurring during growth and puberty may limit the applicability of these mechanisms to pediatrics (137).

2.3.4.2 Fatty Acids

Dairy fat contains fatty acids with suspected health benefits such as conjugated linoleic acid (CLA), alpha-linolenic acid (ALA), *cis* and *trans* palmitoleic acid and butyric acid. One potential mechanism by which dairy fat may have beneficial effects on cardiometabolic risk is by decreasing chronic inflammation (30).

In a cross-sectional study conducted with 494 adolescents aged 15 to 18 years, Abreu et al. examined the association between dairy products consumption and cardiometabolic risk factors (18). They assessed fasting glucose and insulin, TC, HDL-c, TGs, systolic blood pressure, body fat, and cardiorespiratory fitness. Adolescents with high milk intake (but not cheese, yogurt or total dairy products which includes the combined consumption of milk, cheese and yogurt) had lower cardiometabolic risk components score (TGs, HOMA-IR, systolic blood pressure, %BF and cardiorespiratory fitness), compared with those with low milk intake (10.6% vs 18.1% combined risk score, $p = 0.026$). This outcome may be explained by the effects of calcium on body fat metabolism as described above, but likely also because of the location of the study, the Azores Islands, which has a constant temperate Atlantic climate. In terms of the latter, the weather allows for milk production from grazing cows all year long (149). It has been proposed that the milk fat produced from these cows is richer in unsaturated fatty acids, including conjugated isomers of linoleic acid, trans-octadecenoic acids and butyric acid (30). CLA has been associated with improving dyslipidemia and the proinflammatory state related to obesity and MetS (150–152). Butyric acid may also have relevant effects on metabolic health and body mass (153), and chronic inflammatory disorders in the gastrointestinal tract (154), as it plays an important role in gut health (155).

2.3.4.3 Protein Bioactive Peptides

Protein bioactive peptides may positively affect the cardiometabolic variables by improving the satiety response, regulating insulinemia, blood pressure and body composition (29). In regards to the satiety response, it has been suggested that the consumption of whey protein leads to appetite suppression by, a) the bioactive peptides (primarily glycomacropeptide [GMP]); b) the release of amino acids (primarily branched-chain amino acids, especially L-leucine) after digestion; and c) a combined action of these two mechanisms (29). Some studies have reported that GMP stimulates the release of cholecystokinin (CCK), which may enhance the satiety response in rats (156). Additionally, α-lactoalbumin may promote the synthesis of glucagon-like peptide 1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP). These effects, concomitant with the suppression of ghrelin secretion, may contribute to the appetite suppressing effect of dairy protein, thus promoting weight control (157).

Some observational studies in men and women from the U.S. have suggested that dairy consumption may lower the incidence of T2D (143,158). These effects can be explained by the increased insulin response, decreased glycemic fluctuations, increased secretion of GIP and GLP-1 triggered by milk proteins (described above), and by fatty acids such as tans-palmitoleic acid (trans-16:1n-7) found in dairy fat (157).

It is also suggested that dairy consumption may improve blood pressure through bioactive peptides made from proteins in fermented dairy foods (produced by the microbiota in the foods) (159). Pal and Ellis showed that the intake of 54g/d of whey protein for 12 weeks leads to a reduction in systolic and diastolic blood pressure in OW/OB adults (160). Xu et al published a meta-analysis of RCT of milk tripeptides

on blood pressure in prehypertensive and hypertensive participants (161), with similar results as Pal and Ellis (160). Two such bioactive peptides include valine-proline-proline (Val-Pro-Pro) and isoleucine-proline-proline (Ile-Pro-Pro). They have angiotensin-converting enzyme (ACE) inhibiting activity, which may lead to the normalization of blood pressure and reductions in arterial stiffness and endothelial dysfunction (159). However, also as explained above, there is no evidence of these mechanisms in children and adolescents. More research is needed addressing the mechanistic effects of dairy on cardiometabolic parameters in pediatric populations.

2.4 GLUCOSE

Maintenance of a normal plasma glucose concentration requires glucose uptake and utilization by tissues, and endogenous glucose production or dietary glucose delivery (162). Circulating glucose is derived from three sources: intestinal absorption of glucose in the fed state, glycogenolysis and gluconeogenesis. Glucose is stored as glycogen in some tissues (e.g. muscle, liver), it also undergoes glycolysis to pyruvate, and in the liver and kidneys, glucose is released into circulation by glucose-6-phosphatase (163).

In the fasted state, plasma glucose concentrations are relatively stable and rates of glucose production and utilization are equal. Differently, after a meal (the post-prandial state), glucose absorption is enhanced which promotes exogenous glucose delivery to the circulation. As glucose is absorbed, muscle, liver and fat tissues accelerate its usage, and endogenous glucose production is decreased. As exogenous glucose is delivered to the tissues, plasma glucose concentration returns to fasting levels (the post-absorptive state) (164) (Figure 6).

Insulin is responsible for the regulation of blood glucose utilization and glucagon is the main regulator of glucose release from the liver into circulation (162). Both hormones act to maintain glucose homeostasis. Glucagon is a hormone produced by pancreatic alpha cells, and it partially controls glycogenolysis and gluconeogenesis. During the first 6-8 hours in the post-absorptive state, glucose is initially available by glycogenolysis, which is the breakdown of glycogen in the liver. But after longer periods of fasting, gluconeogenesis is then activated in the liver to produce and release glucose into the bloodstream (165). Then, ingestion of carbohydrates elicits a prompt rise in glucose and insulin concentrations, and a decrease in glucagon concentration. After reaching a post-prandial peak, circulating glucose slowly decreases during the next several hours, eventually returning to fasting levels where insulin is suppressed and glucagon is stimulated (163) (Figure 5). Fasting glucose cut-off concentrations for children and adolescents are shown in Table 7.

Table 7. Fasting blood glucose for children and adolescents. Retrieved from (166).

Normal	**Prediabetes**	**Diabetes**
<5.6 mmol/L	5.6 - 6.9 mmol/L	>7 mmol/L

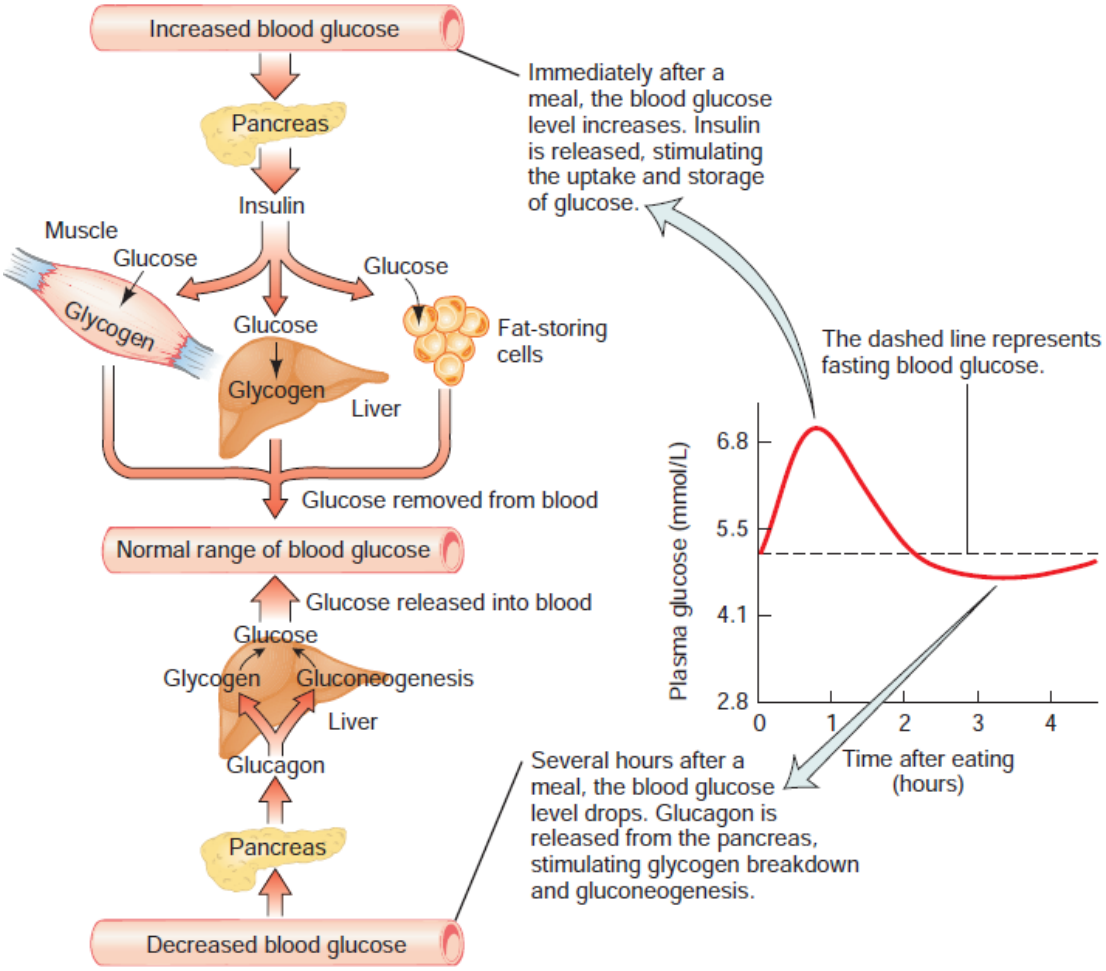

Figure 5. Blood-glucose regulation. Blood-glucose levels are regulated by insulin and glucagon (47).

2.4.1 Hyperglycemia

Hyperglycemia is a metabolic condition characterized by abnormally high levels of glucose in circulating blood (62). Hyperglycemia can occur from the consumption of carbohydrates, the absence of insulin or the delay of its action, or overstimulation of glucagon to produce glucose (62,166). An accumulation of abdominal fat contributes to the desensitization of tissues to insulin, known as peripheral tissue insulin resistance (167). Insulin resistance inhibits the uptake of glucose by insulin sensitive tissues (e.g. skeletal muscle). Increased abdominal fat also impairs the ability to suppress endogenous glucose production (168,169).

Additionally, while tissues are less responsive to insulin, the body secretes more of it to try to overcome this desensitization. In doing so, it stimulates an increased anabolic state which increases lipogenesis and storage (170). These physiological alterations may lead to exacerbations of fat deposition, hyperglycemia as well as hyperinsulinemia (168,171). The relationship between hyperglycemia, insulin resistance and diabetes will be discussed further in section 2.5.1.

2.4.2 Glucose Transporters

Glucose can enter cells in both an ATP-independent and dependent manner by glucose transporter proteins (GLUT). The transporter proteins enable different cell types to utilize glucose according to their functions (172). For instance, most brain cells have GLUT-1 as the main transporter, and can move glucose intracellularly without requiring insulin, and at very low levels of circulating glucose (172). On the other hand, muscle cells and adipose cells have GLUT-4 as their principal transporter, which is insulin and/or contraction (in muscle) dependent. This enables adipose tissue cells, whose function is to store excess energy, to respond to the higher glucose levels characteristic of the fed state, via insulin, by taking up glucose (and fat) increasing lipogenesis and suppressing lipolysis. However, when glucose and insulin levels fall to fasting levels, glucose no longer enters the cells. Lipolysis is then promoted and fatty acids and glycerol are released into circulation for fuel or gluconeogenesis (172).

GLUT 4 transporters are also stimulated to take up glucose in the skeletal muscle by exercise. Davis et al. conducted a RCT in OW/OB children and showed that a regular schedule of 20-40 min of aerobic exercise 5 day/week for 13 weeks significantly improved insulin sensitivity ($p = 0.01$) (measured by insulin area under

the curve using an oral glucose tolerance test) and decreased visceral fat (p <0.001) (173). Similarly, Alberga et al. demonstrated in a systematic review that resistance training has many beneficial metabolic benefits, including improved insulin sensitivity, increased glucose utilization and improved lipid profiles; processes that may be impaired in childhood obesity (96). Researchers attribute improvements in insulin sensitivity through increased glucose utilization as resistance exercise enhance the level of localized muscle contraction and provide a further stimulus to glucose transporter proteins into the cell (174,175).

2.5 INSULIN

Insulin is the principal hormone responsible for glucose homeostasis and it is secreted by pancreatic beta cells (62). It is an anabolic hormone that stimulates glucose influx into body cells, and promotes other anabolic processes including muscle protein synthesis, glycogen synthesis and storage in liver and muscle, and fat storage in adipocytes (62,71). Insulin has a major role in the development of diabetes and obesity (62,170,174). Obesity contributes to the development of T2D by perpetuating insulin resistance which can lead to pancreatic beta cell failure (see section 2.5.2 for further explanation). T2D can also contribute to the development of obesity as a result of metabolic changes in adipose tissue (176,177). To understand the relationship between insulin and T2D, it is necessary to explain insulin resistance first, and its role in the development of metabolic disorders.

2.5.1 Insulin Resistance

Insulin Resistance represents an insensitivity of peripheral tissues (e.g. muscle, liver, fat) to the effects of insulin, that is, when tissues that normally respond to insulin become less responsive and do not take up glucose as readily. Consequently, glucose is left in circulation and blood glucose levels rise (hyperglycemia) (62). Well-functioning pancreatic beta cells have a normal capacity to produce insulin. However, as insulin resistance worsens, beta cells continually stimulate insulin production and release in an attempt to decrease hyperglycemia, but remain ineffective (178,179). This also leads to an additional state called hyperinsulinemia (high concentration of blood insulin) (180). The constant demand on the beta cells to secrete high levels of insulin can eventually lead to beta cell dysfunction. The combination of beta cell dysfunction and peripheral tissue insulin resistance perpetuates the state of T2D (181). As this process continues, progressive failure of the beta cell compensatory response in the presence of insulin resistance, leads blood glucose concentrations to rise, first to pre-diabetes levels (impaired glucose tolerance and impaired fasting glucose) and eventually to levels consistent with T2D (62,163). The progression from normal blood glucose to diabetes is illustrated in Figure 6. T2D develops as a result of insulin resistance and beta cell failure. When the pancreas is able to fully compensate its secretion of insulin, *normal glucose levels* are restored. However, insulin secretion in the blood is high, in a *hyperinsulinemia state* (Figure 6, phase A). Insulin release may not fully compensate for increases in blood glucose concentration if peripheral tissues become insensitive to the effects of insulin. In this case, blood glucose levels go up, first to *pre-diabetic levels* (Figure 6, phase B) and lastly to levels that are suggestive of *T2D* (Figure 6, phase C). When beta-cells fail, there will not be enough cells to maintain insulin release, which leads insulin to drop to levels below normal, in a state

of *hypoinsulinemia* accompanied by a state of hyperglycemia (Figure 6, phase C) (62).

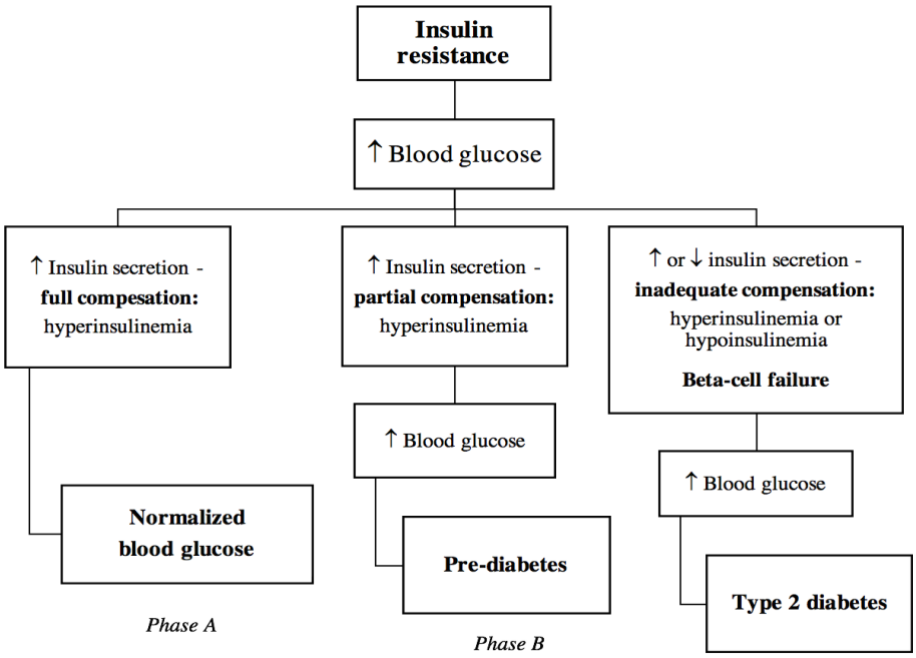

Figure 6. Development of Type 2 Diabetes. Adapted from (47).

According to the Canadian Diabetes Association (CDA), about 11 million people had diabetes in 2016, and it is expected to increase to 13.9 million by 2026 (182). Among children and adolescents, the incidence of T2D has increased in the last twenty years, with over 95% of diabetic children being OW/OB (183). It is shown that insulin resistance can already develop with weight gain in children within the normal range of body mass (184). This shows that insulin resistance starts early in life and can precede other metabolic issues, like pre-diabetes, T2D and MetS. Thus, identification of insulin resistance in the early stages of life is a strategy to target high risk children and prevent various metabolic disorders associated with progressive obesity such as early atherosclerosis, hypertension, fatty liver disease, dyslipidemia and polycystic ovarian syndrome from occurring during childhood and adulthood

(184,185). Obesity has been associated with insulin resistance and related complications (170). A cross-sectional study from Srivasan et al. using data from the Bogalusa Heart Study showed that a higher BMI was associated with higher fasting insulin levels in childhood and youth, and with higher fasting glucose levels in young adulthood (186). Other authors have suggested that a higher BMI-percentile is associated with increased insulin resistance in children, which is an initial step in the pathogenesis of T2D (71,184). In a representative subsample of adolescents from the United States aged 12–19 years who participated in the NHANES, obesity was by far the most significant determinant of insulin resistance, independent of sex, age, or race/ethnicity (184). Strategies to manage childhood obesity are necessary to avoid future development of insulin resistance, T2D and other associated metabolic disorders worldwide.

2.5.2 Insulin and Lipid Metabolism

The relationship between insulin and glucose is well known, however insulin also plays an important role in the regulation of lipid metabolism. When blood glucose is high (i.e. post-prandial state), insulin is also increased. Insulin stimulates the enzyme lipoprotein lipase (LPL). LPL breaks down the TGs in chylomicrons (which come from the small intestine) and in VLDLs (produced by the liver), so that fatty acids can enter the adipocytes, where they reassemble into TGs and are stored in adipose tissue (62). When fat is needed for use (i.e. in the post-absorptive state), adipose tissue releases free fatty acids (FFAs) into the circulation where they can be taken up by cells throughout the body to produce ATP (62). This process is stimulated by another enzyme called hormone-sensitive lipase (HSL) (Figure 7). The liver can

also take up the FFAs and glycerol from circulation and package them back into VLDL, which is then secreted by the liver again into the blood.

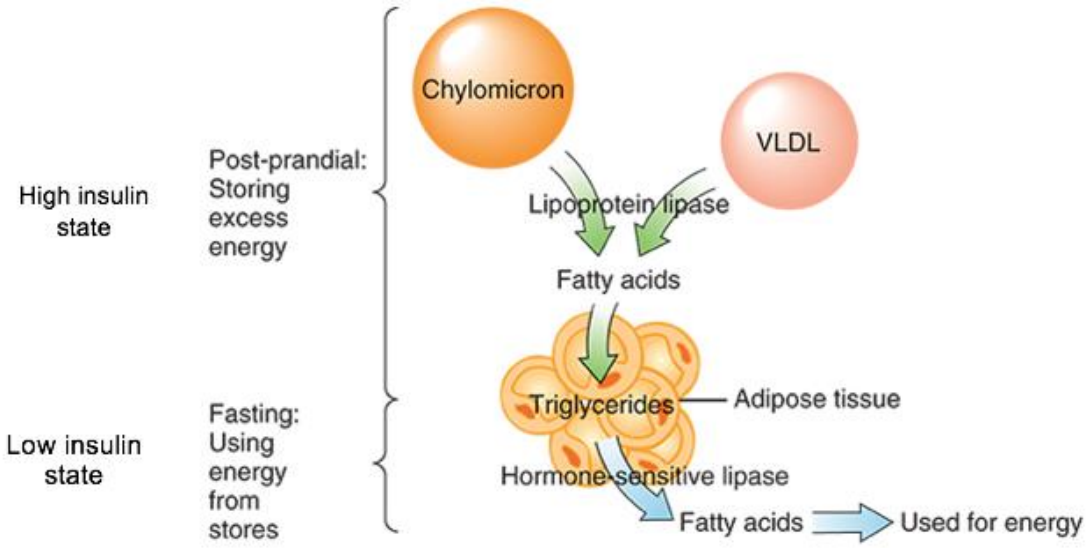

Figure 7. Storing and recovering energy from fat. Insulin mediate the action of the enzymes lipoprotein lipase and hormone-sensitive lipase to store and remove triglycerides in adipose tissue, respectively. Retrieved from (47).

Overall, when insulin is activated it promotes anabolic processes such as: a) stimulating LPL for storage of TGs in adipose tissue: lipogenesis, and b) suppressing HSL, which in turn restrains the release of FFAs from adipose tissue: preventing lipolysis. Once blood glucose is normalized and insulin is low, the following processes predominate such as: a) inhibition of LPL causing TGs to not be taken up for storage in the adipose tissue: inhibition of lipogenesis, and b) stimulation of HSL causing a release of FFAs into circulation: lipolysis. Liver and muscle cells then take up the FFAs and use them as fuel (62,170,187).

Individuals with insulin resistance have higher levels of circulating FFAs than people who are insulin sensitive because the usual suppressive effect that insulin has on HSL is diminished at the adipose tissue, thus allowing HSL to breakdown TGs and

release them into the blood in the presence of high insulin levels (62,170). Normally, in the liver, insulin stimulates the uptake of glucose (for glycogenesis) and inhibits gluconeogenesis (synthesis of glucose from non-glucose precursors). However, in the insulin resistance state glycogenesis is impeded (because glucose cannot enter the liver cells) and gluconeogenesis occurs excessively, both of which lead to hyperglycemia (165). The liver also synthesizes TGs and VLDL from FFAs. Insulin inhibits the release of VLDL, but in the insulin resistance state this effect is decreased and circulating VLDL increases (170,188). Normally, muscle cells take up glucose (in the fed state – high insulin) and fatty acids (in the fasting state – low insulin) for energy. If the individual is insulin resistant, the uptake of glucose in muscle cells is decreased which contributes to hyperglycemia, and there is an increased storage of TGs in this tissue (170,188,189)

Excessive amounts of adipose tissue throughout the body (obesity) promotes a greater release of FFAs in the circulation (62,167). The liver and muscle take up and oxidize some of these FFAs to produce energy and some are stored as TGs. In some inactive, OB individuals, the amount of FFAs taken up may be excessive. In this case, the excess is channelled into different metabolic pathways, producing products that can cause insulin resistance. This effect of excess uptake leading to alternative metabolic pathways is known as lipotoxicity. Similar effects occur in the liver and the beta-cell of the pancreas which can lead to beta-cell dysregulation and eventually insulin resistance (62,167). Obesity also produces an inflammatory effect by inducing an increase in the number and size of adipocytes, which causes an infiltration of macrophages into this tissue that release proinflammatory cytokines. This chronic systemic inflammation interferes with insulin homeostasis, eventually promoting insulin resistance (62,167). These imbalances together result in metabolic

impairments that may start in childhood and progress into adulthood (1). Early identification of children with greater cardiometabolic risk is vital to prevent future complications.

2.5.3 Assessing Insulin Resistance and Insulin Sensitivity

The standard technique for assessment of insulin sensitivity/resistance is the hyperinsulinemic euglycemic clamp. Although this method has been used to study insulin sensitivity/resistance and insulin secretion during childhood, it is complicated, quite invasive and expensive, as it requires 3-hours of continuous administration of both glucose and insulin intravenously (190). For this reason, using minimally invasive, simple and reliable measures of insulin resistance are important to monitor disease risk in youth. Indices such as the quantitative insulin sensitivity check index (QUICKI) and the homeostatic model assessment - insulin Resistance (HOMA-IR) have been used in large studies (179,191) and clinically (178,192) to determine the degree of insulin sensitivity and resistance, respectively, in children and adolescents. HOMA-IR is calculated using the product of fasting concentrations of glucose (mmol/L) and insulin (mU/L) and divided by a constant of 22.5. This method has been well correlated with the euglycemic clamp technique in the seminal study by Matthews et al., (193). The values of insulin resistance obtained from HOMA-IR were well correlated with the hyperinsulinemic-euglycemic clamp in 12 normal weight men ($r = 0.83$, $p<0.01$), in 11 diabetic men ($r = 0.92$, $p < 0.0001$) and in both groups together ($r = 0.88$, $p < 0.0001$) (193).

QUICKI has been used to determine insulin sensitivity in clinical investigations. The index is derived by calculating the inverse sum of logarithmically

expressed fasting glucose and insulin concentrations. As fasting insulin levels decrease, QUICKI values increase (194). Keskin et al. compared the HOMA-IR and QUICKI methods using results from oral glucose tolerance tests (OGTT) in 57 OB children and adolescents (195). The OGTT consists of blood draws at 0, 30, 60, 90 and 120 minutes after oral glucose administration to measure insulin and glucose. The participants were divided in 2 groups, insulin resistant (n=25) and non-insulin resistant (n=32). They found significant differences between HOMA-IR and QUICKI between the 2 groups ($p < 0.05$ for both). The authors performed a receiver operating characteristic (ROC) scatter plot based on insulin resistance and sensitivity to analyze sensitivity and specificity of HOMA-IR and QUICKI. HOMA-IR was shown to be more sensitive and specific as a measure of insulin resistance compared to QUICKI as a measure of insulin sensitivity in children and adolescents (195). In addition, this study confirmed a HOMA-IR cut-off point to determine insulin resistance in children and adolescents. The cut-off of 3.16 yielded a sensitivity of 76% and a specificity of 66% (195).

2.6 LIPIDS

Obesity is associated with dyslipidemia (109). Dyslipidemia is a group of disorders of lipoprotein metabolism, including its overproduction and/or deficiency of certain lipoproteins and lipids in the blood (196). Before getting into the discussion of lipid disorders and obesity, it is necessary to describe how these components are normally metabolized in the tissues throughout the body.

2.6.1 Lipid Transport and Delivery

In the post-prandial state, short- and medium-chain fatty acids are transported from the small intestine to the blood. Long-chain fatty acids and cholesterol must be incorporated into chylomicrons before entering the bloodstream (Figure 8, step 1). Chylomicrons in the bloodstream encounter LPL on vessel walls which breaks down TGs into fatty acids and glycerol. The fatty acids then enter the surrounding cells to be stored or used as energy (Figure 8, step 2). Chylomicron remnants then go to the liver and are disassembled (Figure 8, step 3). TGs are reformed in the liver and are incorporated into lipoproteins; VLDL being the first lipoprotein from the liver. VLDLs transport lipids out of the liver and deliver TGs to tissue cells (Figure 8, step 4). Once TGs are removed from VLDL, a smaller, denser, intermediate-density lipoprotein (IDL) remains. Approximately two-thirds of the IDLs return to the liver, and the rest is converted into LDL. LDL primarily consists of cholesterol and is the main delivery system of cholesterol to the cells (Figure 8, step 5). Apoprotein B (apoB), a protein on the surface of LDL, must attach to a LDL-receptor, then LDL can be taken up by the cells where cholesterol and other components can be used (Figure 8, step 6). HDLs participate in reverse cholesterol transport by circulating in the blood collecting cholesterol from other lipoproteins and body cells, and return it to the liver for repackaging or disposal, or transfer it to organs with a high cholesterol requirement, such as those involved in steroid-hormone synthesis (Figure 8, step 7) (62).

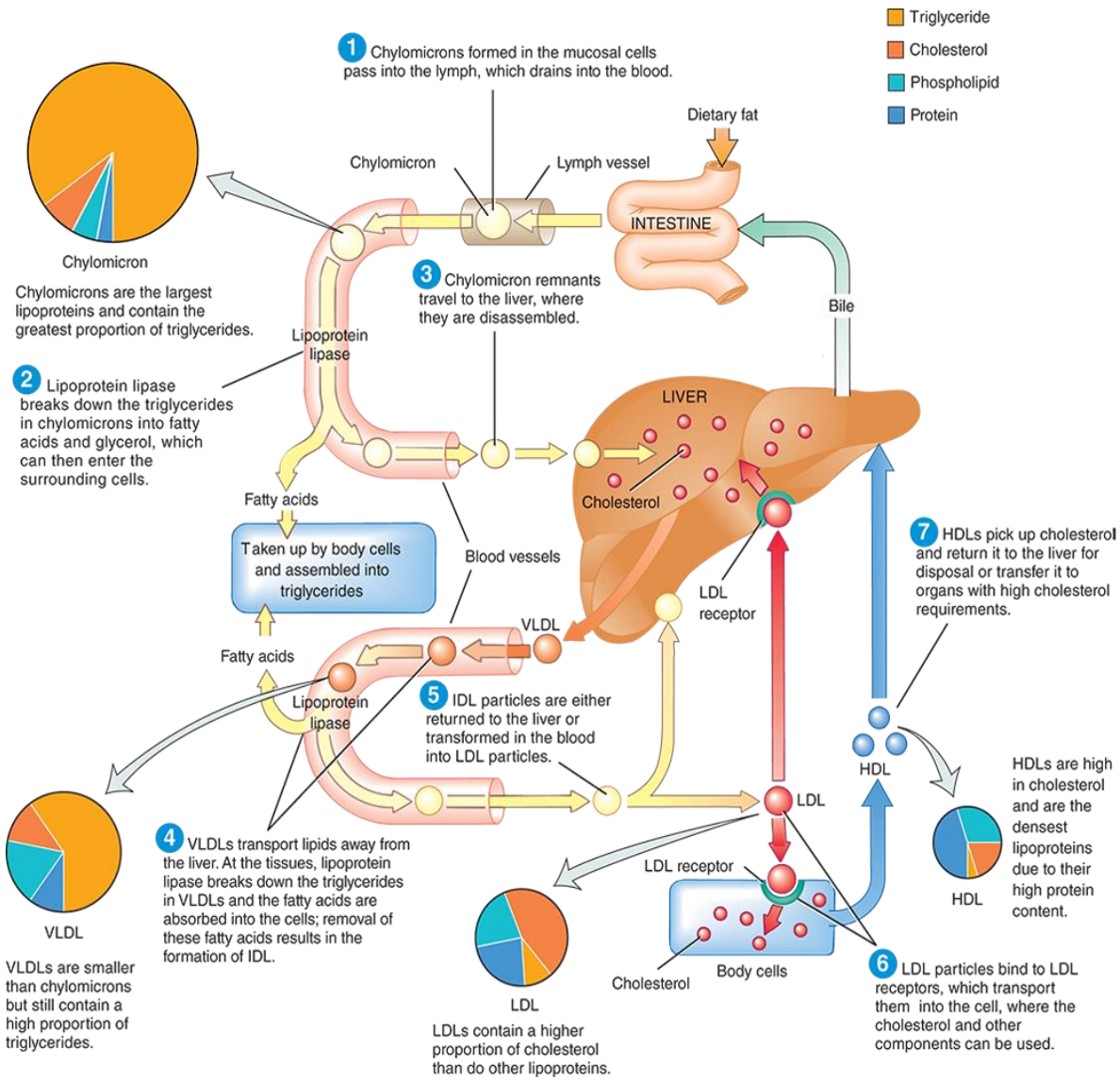

Figure 8. Lipid transport. Retrieved from (47).

2.6.2 The Role of Dyslipidemia, Obesity and Development of CVD

Childhood obesity can increase the risk of CVD due to the abnormal levels of lipoproteins that circulate in the blood (114). As discussed in previous sections, the greater the adipose tissue mass (and the level of insulin resistance), the greater the release of FFAs. These are taken up by the liver and synthesized into TGs, which are packaged as VLDLs and secreted. Consequently, an OB individual will tend to have increased levels of VLDL in the blood compared to a lean individual (197,198). Over

time, the elevated concentration of serum VLDL promotes the development of CVD and may lead to atypical lipoprotein metabolism (196). Cholesterol from HDL is not taken up by the liver as it normally would, but transferred back to VLDL, which results in a cholesterol-depleted HDL. The depleted-HDL molecule is cleared from the blood rapidly, decreasing the levels of circulating HDL (159). In addition, high levels of VLDL cause abnormal transfers of TGs from VLDL to LDL. Consequently, this TGs-enriched-LDL particle, rather than being directly taken up by the liver, interacts instead with hepatic lipase (an enzyme that acts like LPL but is found in the liver) to remove the TGs, leaving in the blood an LDL particle that is smaller in size than the original LDL particle and richer in cholesterol. This particle is called small dense [sd]-LDL. The sd-LDLs tend to be more atherogenic and accumulate more easily in blood vessel walls due to their small size, and are more rapidly oxidized. Hence, the smaller size and faster oxidation of sd-LDL particles promote the development of CVD and atherosclerosis more readily than normal LDL (62).

In the Bogalusa Heart Study, 58% of the OW children presented with at least one risk factor for CVD (52), which may suggest that excess adiposity is associated with early vascular complications, although it is not the only risk factor. OW is also predictive of accelerated atherosclerosis and of early cardiovascular events in adult life (105). Studies reveal that cardiovascular complications begin in childhood (202,203) and endothelial damage has been noted in children with lipid abnormalities (204). In two studies, the 'Pathobiological Determinants of Atherosclerosis in Youth Study' and the 'Bogalusa Heart Study', high TGs and low HDL were strongly correlated with evidence of premature atherosclerosis in youth (205–207). Thus, prevention and management of childhood dyslipidemia and obesity are important for

the prevention of future cardiometabolic diseases and complications (196). Table 8 shows the reference and cut-off values for blood lipids in children and adolescents.

Table 8. Acceptable, borderline, and high plasma lipid concentrations (mmol/L) for children and adolescents. Adapted from (115).

	Acceptable	**Borderline**	**High**
TC	< 4.40	4.40 - 5.15	> 5.18
LDL-c	< 2.85	2.85 - 3.34	> 3.37
TGs			
0 - 9 years	< 0.85	0.85 - 1.12	> 1.13
10 - 19 y	< 1.02	1.02 - 1.45	> 1.47
HDL-c	> 1.17	1.04 - 1.17	< 1.04

TC: total cholesterol, LDL: low density lipoprotein, TGs: triglycerides, HDL: high density lipoprotein.

In addition to standard lipid profile measures, the TGs to HDL-c ratio (TGs:HDL-c) has emerged as a useful tool to diagnose and monitor lipid levels in patients with CVD risk factors (208). In adults, the TGs:HDL-c has been shown to be a strong predictor of coronary heart disease (208,209). Quijada et al. showed that the TGs:HDL-c was useful in determining pre-pubertal children at risk for obesity, dyslipidemia, MetS and hypertension (210). Giannini et al. demonstrated that the TGs:HDL-c is associated with insulin resistance, particularly in white boys and girls, but not significantly in Hispanics or African Americans youth (211).

Lipoprotein ratios reflect the interactions between lipid fractions more accurately than isolated lipid values for assessment of CVD risk (208). In children, an elevated TGs:HDL-c is associated with insulin resistance, non-alcoholic fatty liver disease and cardiometabolic risk factors, and has been used as a marker to monitor these conditions (114,208,212,213). In individuals with insulin resistance, TGs levels

are normally high and HDL-c is low. Thus, the TGs:HDL-c ratio has been proposed to be an alternative assessment of insulin resistance, with a higher ratio demonstrating a lower health status, as it would show a high concentration of circulating fats and/or low concentration of 'healthy cholesterol' (HDL-c) (214). A TGs:HDL-c ratio of ≥2 has been proposed to be closely associated with increased cardiometabolic risk (insulin resistance, high waist circumference, high blood pressure, impaired fasting glucose, high white blood count and MetS) in children and adolescents (212).

2.7 OBJECTIVES AND HYPOTHESES

The overall objective of this thesis was to examine metabolic variables in OW and OB adolescent girls before and after a 12-week intensive lifestyle modification program including exercise training and healthy nutrition advice with and without the consumption of the recommended number of dairy products. The specific objectives of this thesis were to determine whether dairy consumption during a weight management intervention combining healthy eating and exercise affected:

- fasting insulin levels.
- fasting glucose levels.
- fasting TGs, TC, HDL-c and LDL-c levels.

The hypotheses of this thesis were that the metabolic variables of fasting glucose, insulin, TGs, TC and LDL-c would decrease and/or normalize, and HDL-c would increase and/or normalize in OW and OB adolescent girls following a non-energy restricted, 12-week weight management, lifestyle modification intervention combining healthy eating and exercise training, with and without dairy consumption.

It was also hypothesized that those consuming the recommended amount of dairy products would show greater improvements in lipids, insulin and glucose compared to those not consuming dairy products during the intervention.

CHAPTER 3

METHODS

3.1 Study Design

This study is part of the larger 'Improving Diet, Exercise And Lifestyle (IDEAL) for Adolescents' study, which is a 12-week randomized, controlled intervention study involving OW/OB adolescent girls. For this thesis, a total of 20 participants were recruited and assigned to one of two groups: Recommended Dairy (RDa) and Low Dairy (LDa). The two intervention groups (RDa and LDa) differed in the amount of dairy consumed (4 svgs/d RDa *vs* 0-1 svgs/d LDa). Participants in both groups underwent the same exercise program and were counselled on healthy eating at the same intervals.

3.2 Participants, Recruitment, Inclusion/Exclusion Criteria

Participants were recruited in the Niagara region by advertising in the local paper, on local radio, in public transit, on local TV stations, social media (Facebook), press release from Brock University and through flyers. We also recruited from pediatric and general practitioner physician clinics in the area and in the local elementary and high schools of the District School Board of Niagara. To be eligible for this study, participants needed to be menarcheal, OW (≥85-97 percentile BMI) or OB (≥97 percentile BMI) [On WHO growth charts (http://www.cps.ca/tools-outils/who-growth-charts)] and between the ages 10 and 18 years. Other general

criteria included low dairy consumption (0-2 servings per day and <700 mg calcium per day), inactive (0-2x/week) and otherwise healthy. Exclusion criteria included allergy to dairy foods or diagnosed lactose intolerance, taking medications related to a chronic condition or that affect bone health, and/or taking vitamin or mineral supplements that were not prescribed by a practitioner. Ethical clearance was obtained from the Brock University Biosciences Research Ethics Board (REB 14-284) and informed consent was obtained from the participants and their guardians.

3.3 Procedures and Consent Process

Interested participants responded by contacting the study office by phone or email. They then answered a series of questions confirming their eligibility to participate. Once deemed eligible, informed consent was sought at the first scheduled visit. After receiving informed consent, each participant completed a general health questionnaire to document medical history and medication use (Appendix A). After screening the participants, and all entry criteria had been met, they were stratified by BMI-for-age percentile (85-97th or ≥97th) (OW or OB) to ensure that an equal number of participants from each BMI category were in all groups, and then randomized to one of the two groups (LDa, RDa). Subsequently, the preliminary visits for baseline testing were scheduled before the intervention commenced. All testing took place at Brock University in the *Nutrition, Exercise and Lifestyle Improvement Laboratory*.

During the first visit, participants arrived at the laboratory in the morning (between 8:00 and 10:00 am) after an overnight fast. A venous blood sample was collected. Anthropometric and body composition measures were then performed including height, body mass, %BF, LM, FM and waist circumference. Participants

were asked to fill out a 7-d food record (FR) to verify their low dairy/calcium intake and to learn about their daily diet prior to commencing the study.

Following this visit, participants came back to the laboratory for an exercise introduction session where the parent and participant met their personal trainer, went over the exercises that were going to be performed, and outlined an exercise schedule for the next 12 weeks. Pedometers (FitBit Zip) and iPod shuffles were also provided to the participant during this visit. After the exercise introduction session, participants had their first diet consultation with a registered dietitian (week 0). The dietitian reviewed the baseline 7-d FR with the participant and their parent/guardian, and gave instructions for beginning the diet protocol. If the participant was randomised to the RDa group, dairy products were provided during this visit.

3.4 Diet and Exercise Intervention for 12 Weeks

3.4.1. Diet Intervention

The diets were designed for weight maintenance rather than for energy restriction. Energy expenditure was calculated per participant using predictive equations from the Academy of Nutrition and Dietetics for OW and OB girls with a sedentary activity factor (http://www.andeal.org/topic.cfm?cat=3060). This was used to prescribe a diet for weight maintenance based on participant's age, height and body mass. LDa and RDa groups differed only in the type of protein consumed (and associated nutrients). The ratio of macronutrients was 20:55:25 (Protein:Carbohydrate:Fat), and participants were counselled on achieving a healthy dietary intake consisting of: fruit, vegetables, fibre, whole grains, lean meats and meat alternatives. Also, they were asked to avoid processed foods, high 'bad'

(trans/saturated fat [SFA]) fat foods, sugar-sweetened beverages, pastries and confection.

The LDa group maintained their low dairy intake of 0-2 svgs/d, and consumed protein from sources other than dairy, including: meat, egg, fish, chicken, legume and grains. They were asked to refrain from consuming calcium-fortified beverages/foods. Meanwhile, the RDa group consumed 4 svgs/d of dairy as recommended in Canada's Food Guide (Health Canada, 2016), including: 2 cups of milk (white and chocolate 1%), 2x100g cartons of 0% or 2% MF Greek yogurt (any flavour) and 50 g of cheese. All dairy products were provided to the participants. Participants picked them up from the *Nutrition, Exercise and Lifestyle Improvement Laboratory* on a weekly basis. Because of the intake of dairy, the RDa group was consuming over half of their daily protein from dairy products. In addition, they were consuming at least 1250 mg of calcium and 240 IU of vitamin D, representing 96% (1250/1300 mg) and 40% (240/600 IU) of the RDAs for these nutrients, respectively. Participants were instructed not to take any vitamin or mineral supplements during the study.

Participants received individualized diet counselling by a registered dietitian, 5 times during the study (weeks 0, 2, 4, 8, 12). The initial 7-d FR was analyzed using the *Food Processor* Diet analysis program by ESHA (ESHA Research) and served as a starting point on which the diet counselling was based. Participants were provided with an individualized eating plan outlining their required macronutrient intakes in food group servings corresponding to their daily energy requirements. Participants provided 3-d FRs (7-d FR in week-12) before each counselling session to track compliance with the nutrition protocol. They received feedback about their intakes in the following diet consult. The same investigator analyzed all FRs using ESHA.

3.4.2. Exercise Training Intervention

Participants underwent exercise training over the 12 weeks, 3 times/week, at Brock University. On days that participants did not receive formal exercise training, they were assigned various forms of physical activity to achieve a predetermined number of steps during their leisure time. Steps were determined using the pedometers provided. Each formal training session lasted about 60-90 min and consisted of aerobic (e.g. treadmill, stationary bike, stairs), plyometric (jumping) and resistive exercise (e.g. thera bands, free weights, and body-weight exercises). Each session consisted of a warm-up (5 min), aerobic exercise (25 min), resistive exercise (20 min), and a cool down with stretching (10 min). The training sessions followed the principles of progressive overload (starting at 50-60% of maximal ability, based on baseline testing, and progressively increasing the intensity or load) and were facilitated by trained study personnel (students and/or volunteer personal trainers). The volunteer trainers completed resistance and aerobic exercise log sheets and participants completed the pedometer log sheet to be checked frequently by study personnel to ensure compliance. Both groups consumed a drink immediately post exercise. The RDa group had 1 cup of 1% chocolate milk, and LDa group had 1 cup of a non-dairy, vitamin D- and calcium-free, carbohydrate-based drink. These drinks were counted as part of their daily consumption.

3.5 Measurements

3.5.1 Anthropometry and Body Composition

Anthropometric and body composition assessments took place at 0, 6 and 12 weeks. All measures of height (cm), seated height (cm), body mass (kg) and body

composition were assessed by the same investigator for each participant. Standing and sitting height were measured using a stadiometer to the nearest 0.1cm with light clothing and no shoes. Body mass, %BF, LM and FM were assessed using the BodyMetrix device which is a hand-held ultrasound probe that measures body fat in different areas of the body (BodyMetrix^{TM} System, BX-2000, IntelaMetrix, Inc., Livermore, CA). Body composition was calculated by measuring subcutaneous fat thickness at 4 sites (triceps, hip, waist and thigh). Waist and hip circumference were measured using a flexible measuring tape to the nearest 0.1 cm at four body sites in duplicate: waist, midline between 11th rib and iliac crest (umbilicus line), high hip line (above iliac crest and below umbilicus), hip line (widest part of the hip, over the gluteus muscles). Each measurement was taken 2x and an average of the two was used. All body composition and anthropometric measures were done by the same investigator. BMI was calculated as weight (kg) divided by height (cm) squared.

3.5.2 Biochemical Analysis

Fasting blood samples were obtained on two occasions (pre- and post-intervention) between 8:00 and 10:00 am after an overnight fast of 10–12 h, using serum, oxalate and non-heparinized tubes. Blood was centrifuged between 30-60 minutes after the blood draw, at 3500 rpm and 4°C for 15-20 minutes. The serum/plasma was separated and aliquoted into 0.5ml polyethylene tubes, being stored at -80°C until analysis.

TC, TGs, HDL-c and glucose were measured using the Alere Cholestech LDX® System (ref. 10-991. San Diego, CA, USA). LDL-c was calculated by the Cholestech LDX® System. This system combines enzymatic methodology and solid-

phase technology. Specifically, the Cholestech LDX® system measures TC and HDL-c by enzymatic methods based on the hydrolysis of cholesterol esters to free cholesterol. Similarly, TGs are measured based on the hydrolysis of TGs by lipase to glycerol and FFAs. For glucose, the system uses glucose oxidase to catalyze the oxidation of glucose to gluconolactone and hydrogen peroxide. The resultant colour in all the reactions is measured by reflectance photometry (215). Serum insulin was analyzed in duplicate using an enzyme-linked immunosorbent assay (ELISA; R&D Systems®. Quantikine ELISA Human/Canine/Porcine Insulin. Catalog no. DINS00, Minneapolis, MN, USA). The average intra-assay coefficient of variation was 3.8%.

3.5.3 Calculations

HOMA-IR uses the product of fasting insulin (mU/L) and fasting glucose (mmol/L) divided by 22.5 to measure insulin resistance (193). Insulin resistance was defined as a HOMA-IR value of >3.16 (195). QUICKI is a variation of HOMA-IR, but it assesses insulin sensitivity by calculating the log transformation of fasting insulin added to fasting glucose (1/(log10 insulin mU/L + log10 glucose mmol/L) (194). The ratio of TGs:HDL-c has been used to predict CVD risk because this ratio is inversely correlated with plasma levels of small, dense LDL particles (212). This ratio has also been correlated with insulin resistance in children and adolescents (214). Our study did not demonstrate significant changes in these indices after the 12-week intervention.

3.6 Statistical Analysis

Statistical analyses were performed using SPSS version 22.0 for Windows (SPSS, Chicago, Illinois, USA). Data are presented at mean +/- standard deviations in the tables. Independent t-tests were used to assess baseline differences between the groups. Two-way analysis of variance for repeated measures (RM ANOVA) were conducted to examine the differences in BMI, body mass, waist circumference, body composition, TC, LDL-c, HDL-c, TGs, insulin, glucose and dietary nutrients (i.e. protein, carbohydrates, total fat, saturated fat, calcium and vitamin D) between the first and second time points (TIME/within effect) and between RDa and LDa groups (GROUP/between effect). Pearson correlations were performed on the change values and percentage change values for BMI, body mass, body composition, serum lipids, insulin and glucose to assess the relationship between them. Significance was assumed at or below an alpha level of 0.05.

3.6.1 Sample size justification

No study has assessed cardiometabolic variables in adolescent girls after increased intakes of dairy products combined with exercise. Only one study carried out in 120 pre-pubertal, OB children (boys and girls) found a significant increase ($p = 0.01$) in HDL-c and a significant decrease in TGs ($p < 0.0001$) after low and high intakes of dairy products for 6 months, however no difference was found between groups (21). Other studies have investigated the effects of a lifestyle intervention (healthy diet and exercise) on cardiometabolic markers, but not combined with different intakes of dairy (see Table 5 in literature review). Therefore, for the sample size calculation, the study by Kelishadi et al. was chosen as its outcomes are most

similar to ours. The sample size calculation was done to see a change in TGs over the intervention between groups. An α -value of 0.05 and a desired power of 0.80 was used. The calculated total sample size was 60 participants, with an effect size of 0.2 units (G*Power, version 3.1). Therefore, with our current sample size we are underpowered to see this effect.

CHAPTER 4

RESULTS

4.1 Descriptive Characteristics

Twenty adolescent girls completed the intervention as of June 2017, and are therefore included in this thesis; nine in the Recommended Dairy (RDa) group who were all considered OB, and eleven in the Low Dairy (LDa) group, where 6 were OW and 5 were OB. Descriptive characteristics of the adolescents in the study sample are presented in Table 9. There were no differences between groups for lipid profile, fasting glucose and insulin and nutritional intake at baseline. However, adolescents in the RDa group had greater body mass (kg), FM (kg), LM (kg) and waist circumference (cm) compared with the LDa group at baseline ($p = 0.03$, $p = 0.02$, $p = 0.04$, and $p = 0.02$, respectively). BMI, waist:height ratio and saturated fat intake were trending towards significance between groups at baseline ($p = 0.08$,$p = 0.06$, and p = 0.06, respectively).

Table 9. Baseline Characteristics of the two intervention groups presented as mean ± standard deviation.

Variables	RDa (n=9)	LDa (n=11)	P-value
Age (years)	16.0 ± 2.2	15.9 ± 2.0	0.93
Height (cm)	165.1 ± 6.5	162.2 ± 4.7	0.31
BMI	33.1 ± 4.4	29.4 ± 4.7	0.08
Body Mass (kg)	89.7 ± 11.2	77.2 ± 12.1	**0.03***
Waist Circumference (cm)	109.6 ± 10.3	97.4 ± 10.9	**0.02***
Waist:Height ratio	0.67 ± 0.07	0.60 ± 0.07	0.06
Body Fat (%)	41.0 ± 3.4	38.3 ± 4.0	0.13
Fat Mass (kg)	36.7 ± 6.8	28.9 ± 6.1	**0.02***
Lean Mass (kg)	52.6 ± 7.5	46.4 ± 5.1	**0.04***
Total Cholesterol (mmol/L)	4.13 ± 0.70	3.93 ± 0.62	0.50
HDL-c (mmol/L)	0.96 ± 0.33	1.18 ± 0.38	0.19
LDL-c (mmol/L)	2.43 ± 0.73	2.23 ± 0.59	0.51
Triglycerides (mmol/L)	1.62 ± 0.86	1.14 ± 0.43	0.15
TGs:HDL-c	2.30 ± 2.16	1.09 ± 0.54	0.14
Glucose (mmol/L)	4.67 ± 0.29	4.65 ± 0.25	0.84
Insulin (mU/L)	21.5 ± 20.6	13.6 ± 5.3	0.29
HOMA-IR	4.52 ± 4.51	2.83 ± 1.18	0.30
QUICK index	0.54 ± 0.08	0.58 ± 0.08	0.40
Calcium (mg/day)	535 ± 156	487 ± 224	0.59
Vitamin D (IU/day)	27.3 ± 28.4	31.9 ± 33.4	0.74
Energy (Kcal/day)	1762 ± 429	1470 ± 356	0.11
Protein (g/day)	79 ± 27	61 ± 19	0.10
Protein (% Energy/day)	18 ± 4	15 ± 3	0.19
Carbohydrate (g/day)	202 ± 60	201 ± 51	0.97
Carbohydrate (% Energy/day)	45 ± 6	50 ± 5	0.10
Total Fat (g/day)	74 ± 23	64 ± 25	0.39
Total Fat (% Energy/day)	37 ± 5	35 ± 4	0.36
Saturated Fat (g/day)	25 ± 8	18 ± 6	0.06

All results are presented as mean ± standard deviation
*Significance from Independent T-Test, significantly different with p-value < 0.05
LDa: low dairy group; RDa: recommended dairy group; BMI: body mass index; HDL-c: high density lipoprotein cholesterol; LDL-c: low density lipoprotein cholesterol; TGs:HDL-c: triglycerides:high density lipoprotein cholesterol; HOMA-IR: homeostasis model assessment of insulin resistance; QUICKI: quantitative insulin sensitivity check index.

4.2 Anthropometrics, Body Composition and Nutrition

Table 10 displays the anthropometric and body composition data for the RDa and LDa groups pre- and post-intervention. There were no significant interactions for any of the body composition measurements. With respect to the daily dietary intake, the RDa group had a significant increase in calcium and vitamin D, and the LDa group decreased calcium intake and increased the vitamin D. Significant interactions were observed for both calcium and vitamin D indicating that the change in the RDa group was greater than the change in the LDa group. As per the study diet protocol, both groups also increased protein intake per day by the end of the intervention, shown by a significant time effect. Lastly, there were significant group effects for protein and saturated fat intake indicating that the RDa group had increased intakes at both time points.

Table 10. Anthropometrics, body composition measures and dietary intake in both groups pre-intervention and post-intervention.

Variables	RDa (n=9)		LDa (n=11)		*P*-value		
	Pre	Post	Pre	Post	Time	Group	Interaction
BMI	33.1 ± 4.4	32.7 ± 5.0	29.4 ± 4.7	28.7 ± 3.8	0.07	0.07	0.65
Height (cm)	165.1 ± 6.5	165.3 ±6.5	162.2 ± 4.7	162.5 ± 4.9	**0.03***	0.28	0.60
Body Mass (kg)	89.7 ± 11.2	88.9 ± 11.7	77.2 ± 12.1	75.4 ± 9.6	0.16	**0.02***	0.57
Waist Circumference (cm)	109.6 ± 10.3	106.3 ± 9.6	97.4 ± 10.9	94.4 ± 9.4	**0.003***	**0.01***	0.89
Waist:Height ratio	0.67 ± 0.07	0.65 ± 0.07	0.60 ± 0.07	0.58 ± 0.06	**0.003***	**0.05***	0.93
Body Fat (%)	41.0 ± 3.4	38.6 ± 3.5	38.3 ± 4.0	36.0 ± 4.0	**<0.001***	0.12	0.92
Fat Mass (kg)	36.7 ± 6.8	34.8 ± 7.2	28.9 ± 6.1	27.2 ± 5.6	**<0.001***	**0.02***	0.79
Lean Mass (kg)	52.6 ± 7.5	54.5 ± 5.3	46.4 ± 5.1	48.1 ± 5.6	**0.01***	**0.03***	0.89
Calcium (mg/day)	535 ± 156	1260 ± 112	487 ± 224	457 ± 186	**<0.001***	**<0.001***	**<0.001***
Vitamin D (IU/day)	27.3 ± 28.4	343.0 ± 98.2	31.9 ± 33.4	39.7 ± 36.4	**<0.001***	**<0.001***	**<0.001***
Energy (Kcal/day)	1762 ± 429	1750 ± 448	1470 ± 356	1594 ± 296	0.64	0.09	0.57
Protein (g/day)	79 ± 27	96 ± 19	60 ± 19	78 ± 15	**0.01***	**0.02***	0.97
Protein (%Energy/day)	18 ± 4	22 ± 4	15 ± 3	20 ± 3	**0.001***	0.06	0.99
Carbohydrate (g/day)	202 ± 59	189 ± 32	201 ± 51	187 ± 48	0.36	0.93	0.97
Carbohydrate (%Energy/day)	45 ± 6	44 ± 6	50 ± 5	45 ± 6	0.08	0.12	0.48
Total Fat (g/day)	74 ± 23	61 ± 18	64 ± 25	62 ± 14	0.34	0.46	0.48
Total Fat (%Energy/day)	37 ± 5	34 ± 7	35 ± 4	35 ± 4	0.43	0.67	0.44
Saturated Fat (g/day)	25 ± 8	25 ± 7	18 ± 6	17 ± 5	0.83	**0.004***	0.84

All results are presented as mean ± standard deviation
*Significance from 2-way repeated measures ANOVA (Group: RDa and LDa; Time: pre-to post-intervention), significantly different with p value < 0.05.
LDa: low dairy group; RDa: recommended dairy group; BMI; body mass index.

4.3 Metabolic Variables

Table 11 displays the metabolic and lipid variables for the RDa and LDa groups separately, before and after the intervention. There were no significant interactions or time effects for any of the variables. However, significant group effects were observed for TGs and TGs:HDL-c ratio.

Table 11. Fasting blood values in both groups pre-intervention and post-intervention.

Variables	RDa (n=9)		LDa (n=11)		P-Value		
	Pre	Post	Pre	Post	Time	Group	Interaction
Total Cholesterol (mmol/L)	4.13 ± 0.70	4.16 ± 0.72	3.93 ± 0.62	3.91 ± 0.75	0.96	0.47	0.77
HDL-c (mmol/L)	0.96 ± 0.33	0.97 ± 0.38	1.18 ± 0.38	1.21 ±0.29	0.65	0.14	0.87
LDL-c (mmol/L)	2.43 ± 0.73	2.47 ± 0.74	2.23 ± 0.59	2.29 ± 0.69	0.54	0.53	0.88
Triglycerides (mmol/L)	1.62 ± 0.86	1.55 ± 0.63	1.14 ± 0.43	0.90 ± 0.32	0.17	**0.03***	0.46
TGs:HDL-c ratio	2.30 ± 2.16	1.99 ± 1.30	1.09 ± 0.54	0.79 ± 0.33	0.17	**0.03***	0.98
Glucose (mmol/L)	4.67 ± 0.29	4.79 ± 0.37	4.65 ± 0.25	4.53 ± 0.28	0.98	0.21	0.14
Insulin (mU/L)	21.5 ± 20.6	16.5 ± 9.7	13.6 ± 5.3	11.3 ± 3.9	0.19	0.14	0.62
HOMA-IR	4.52 ± 5.51	3.56 ±2.17	2.83 ± 1.18	2.27 ± 0.79	0.25	0.12	0.76
QUICKI	0.54 ± 0.08	0.56 ± 0.09	0.58 ± 0.08	0.59 ± 0.04	0.35	0.27	0.95

All results are presented as mean ± standard deviation
*Significance from 2-way repeated measures ANOVA (Group: RDa and LDa; Time: pre-to post-intervention), significantly different with p value < 0.05. define acronyms
LDa: low dairy group; RDa: recommended dairy group; HDL-c: high density lipoprotein cholesterol; LDL-c: low density lipoprotein cholesterol; TGs:HDL-c: triglycerides:high density lipoprotein cholesterol; HOMA-IR: homeostasis model assessment of insulin resistance; QUICKI: quantitative insulin sensitivity check index.

4.4 Correlations

Table 12 displays the significant correlations observed between some variables within all study participants (n=20). The change in TC was positively correlated with the change in waist circumference and the change in waist:height ratio. The change in insulin was correlated with change in waist circumference and waist:height. The change in HOMA-IR was correlated with the change in body mass and waist circumference. QUICKI change was correlated with body mass change and %BF change.

Table 12. Correlations between the change values in all study participants (n=20).

	Weight	**Body Fat %**	**Waist Circumference**	**Waist:height Ratio**
Total Cholesterol	0.38 P = 0.95	0.21 P = 0.38	**0.48*** P = 0.04	**0.47*** P = 0.04
Insulin	**0.53*** P = 0.02	0.38 P = 0.09	**0.49*** P = 0.03	**0.46*** P = 0.04
HOMA-IR	**0.53*** P = 0.02	0.36 P = 0.12	**0.46*** P = 0.04	0.43 P = 0.06
QUICKI	**-0.51*** P = 0.02	**-0.58*** P = 0.008	-0.39 P = 0.08	-0.38 P = 0.10

**P* value < 0.05

HOMA-IR: homeostasis model assessment of insulin resistance; QUICKI: quantitative insulin sensitivity check index

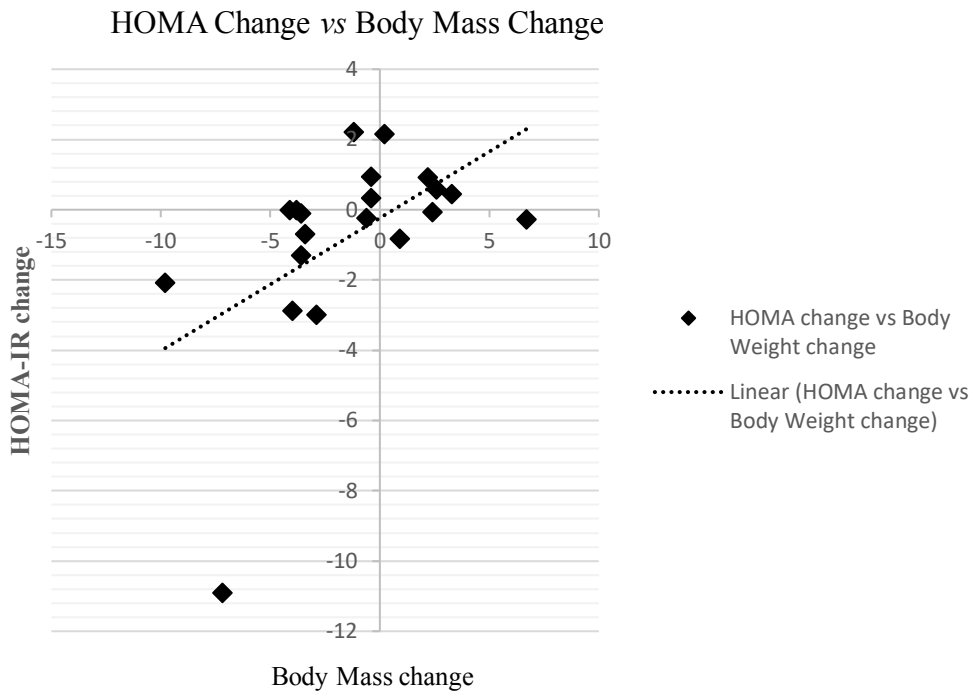

Figure 9. Relationship between HOMA-IR change and body mass change of study participants, r = 0.53, p = 0.02 (n=20).

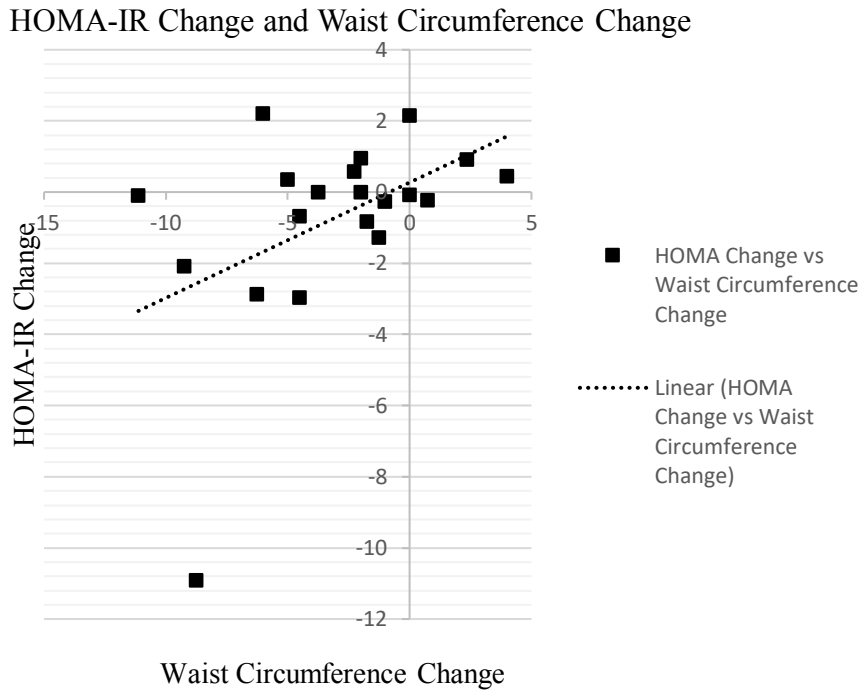

Figure 10. Relationship between HOMA-IR change and waist circumference change of study participants, r = 0.46, p = 0.04 (n=20).

CHAPTER 5

DISCUSSION

The IDEAL for Adolescents study is a RCT that evaluates whether a 12-week lifestyle modification intervention, including a balanced diet for weight management (i.e. no energy restriction) and exercise training (resistance, aerobic and plyometric exercises, 3x/week), with and without dairy consumption (RDa: 4 svgs/d, 1200-1500mg/d Ca vs. LDa: 0-2 svgs/d, <700mg/d Ca), is effective at improving the metabolic profile of OW and OB adolescent girls aged 10-18 years. This is the first study to investigate the association between increased dairy consumption combined with exercise and a healthy diet on the metabolic profile in OW/OB adolescent girls. It was hypothesized that fasting insulin, glucose, TGs, TC and LDL-c levels would decrease in the RDa and LDa groups after the intervention, and that HDL-c levels would increase after the intervention. It was also hypothesized that differences would be observed between the two intervention groups such that the RDa group would show better outcomes. Since only a subset of twenty participants had completed the intervention by June 2017, the analyses in this thesis were carried out on only these participants. Thus, in a subset of 20 participants, results revealed that our intervention did not lead to significant reductions in TC, LDL-c, TGs, insulin and glucose, and increases in HDL-c in participants in either groups. Our analyses, thus far, are underpowered to detect changes in these cardiometabolic variables, which may explain, in part, why we failed to confirm our hypotheses. Another potential reason for this outcome may be explained by the fact that most of the adolescents were

within the normal range for TC, LDL-c and blood glucose at baseline (see Table 7 and Table 8 in literature review for blood glucose and lipids references, respectively), and consequently, major improvements were not likely to be seen after the intervention. Of note, TGs and HDL-c were outside the normal range of values only in the RDa group, however, we did not see greater improvements in this group. We also did not see significant adverse changes in any cardiometabolic marker with or without the addition of 4 servings of dairy per day in an intervention designed for weight maintenance. This suggests, in this small subset of participants, that consuming regular and low-fat dairy foods does not negatively affect blood lipids, glucose or insulin.

Despite the absence of significant changes in certain cardiometabolic markers, we did see improvements in body composition in both groups, such as a decreased waist circumference, waist:height ratio, %BF, FM and increased LM. Moreover, as it was a dietary goal in the study, protein intake per day increased in the RDa and LDa groups. Calcium and vitamin D increased in the RDa group, whereas calcium decreased in the LDa group alone with a small but significant increase in vitamin D. Since the RDa group was consuming 4 servings of dairy per day, we expected to see large increases in those nutrients. The RDa group, during the intervention, was consuming calcium at an adequate level, according to the Recommended Dietary Allowance for this age group which is 1200 mg/d. For the LDa group, the no change/slight decrease in calcium was also expected, as they were instructed to continue consuming 0-1 serving of dairy per day during the study. This reflected their baseline intakes, thus keeping their calcium intake consistent throughout the study. The increase in dietary vitamin D in the LDa group may be explained by the increased consumption of eggs and fish as part of a healthy diet that the dietitian recommended

based on our study guidelines. The vitamin D in the LDa group did not come from dairy foods. With regards to protein intake, it was recommended that both groups increased their intake of this macronutrient from baseline so that it made up 20% of their daily energy intake. The same macronutrient ratios were prescribed and encouraged for both groups. However, the RDa group were getting half of their daily protein from dairy sources and the rest from other healthy sources, whereas the LDa group were getting their protein from meat and meat alternatives (i.e. eggs, beans, chickpeas, quinoa and almonds/nuts), but not dairy.

Research has shown that the presence of unfavourable metabolic markers in OW/OB youth strongly influences the risk of CVD in adolescence, and this tracks into adulthood (52). In this regard, the aim of this thesis, within the larger intervention study, was to explore the effects of a healthy lifestyle modification intervention featuring the combination of positive changes in nutrition and exercise with a focus on incorporating dairy products in the diets of female adolescents. We hoped this would have improved the metabolic profile in these girls. Thus far, our findings suggest that increased dairy consumption, as part of a healthy diet and lifestyle pattern, might be an effective strategy for improving the quality of the diet in OW/OB adolescents (by increasing calcium and vitamin D levels as well as other micronutrients [data not shown]), however, from a subset of 20 participants, we failed to see significant differences between RDa and LDa groups in blood lipids (TC, LDL-c, HDL-c and TGs), fasting insulin and glucose, and anthropometric and body composition components. Despite the absence of significant changes in the metabolic markers, our results demonstrated that when both intervention groups were combined (i.e., time effect in RM ANOVA, Table 10), we did see significant improvements in body composition and anthropometry, presented by the decreased waist

circumference, waist:height ratio, %BF, FM and increased LM. However, again no significant changes were seen between the RDa and LDa groups, thus, the dairy did not amplify/modify these effects in the RDa group, negatively or positively. We can conclude, thus far, in a subset of participants, that improvements in body composition were a result of the overall exercise intervention along with healthy changes in eating patterns (i.e. to include more protein, fruit and vegetables, and less junk food, processed food and SSB), and not from the addition of dairy per se. Also, the current study showed that the RDa group had the same gains in LM as the LDa group. There was a small but significant increase ($p=0.03$) in height over time in both groups (RDa mean change 0.2cm and LDa mean change 0.3cm). This increase could be physiological and/or error in the measurement. Nevertheless, this small average height increase is unlikely to significantly impact our LM or FM results. Thus, it is still believed that the improvement in LM in the study participants is most likely due to the 12-week mixed exercise program and not growth.

Only one other RCT has been carried out assessing the effect of dairy on metabolic markers in a pediatric population. Kelishadi et al. showed that 6 consecutive monthly family-centered educational sessions promoting healthy eating and increased physical activity (by a pediatrician and a nutritionist), with different intakes of dairy, was effective in reducing TGs, fasting insulin, HOMA-IR, and increasing HDL-c. No changes were observed for fasting glucose (21). We did not find similar results to Kelishadi et al., however, it is important to note that the baseline values for TGs and HDL-c in their study were abnormal for all groups (>3.11 mmol/L and <0.97 mmol/L, respectively). Our current study had TGs values around the normal cut-offs at baseline for the LDa group (1.14 mmol/L) and above normal for the RDa group (1.62 mmol/L). The LDa presented normal values for HDL-c (1.18

mmol/L), but the RDa group presented an abnormal/lower mean (0.96 mmol/L). In addition, Kelishadi et al. presented a sample of 40 participants per group (n=120), meanwhile the current study only had a sample of 20 participants total, with 9 in the RDa and 11 in the LDa group.

In summary, our study shows no correlation of increased dairy intake on lipid and glucose homeostasis variables in OW/OB adolescent girls. It is worth mentioning again that our study sample was only a subset of the total sample for the IDEAL for Adolescents Study, therefore we were statistically underpowered for the metabolic variable analyses. Further analysis with a greater sample size is necessary to make conclusions between the relationship of dairy and cardiometabolic markers in our pediatric sample.

5.1 Insulin & Glucose

A systematic review and meta-analysis of RCTs by Ho et al. evaluated the effectiveness of lifestyle modification interventions including a combination of behavioural change, exercise and healthy diet in OW/OB youth (8-16 years) (88). The meta-analysis revealed that comparing the lifestyle modification programs to control groups, the concentrations of fasting insulin lowered after 4 months to 1 year (88). By contrast, in our study, we did not see a significant mean change in fasting insulin or fasting glucose in LDa or RDa groups at week 12. The difference in results of this meta-analysis to ours might be due to study design differences. Ho et al. found significant improvement in fasting insulin in favour of lifestyle modification over 1-year duration (-7.9 mU/L, 95% CI: -10.3 to -5.6, I^2 = 0%) (88), whereas our study was 12 weeks. Moreover, the mean concentration of fasting insulin at baseline was 21.5 ±

20.6 mU/L and 16.5 ± 9.70 mU/L by the end of the intervention in the RDa group, and 13.6 ± 5.30 mU/L at baseline and 11.3 ± 3.90 mU/L at week 12 in the LDa group. As it is observed, the standard deviations are high, particularly in the RDa group, indicating that there is variability (Figure 9).

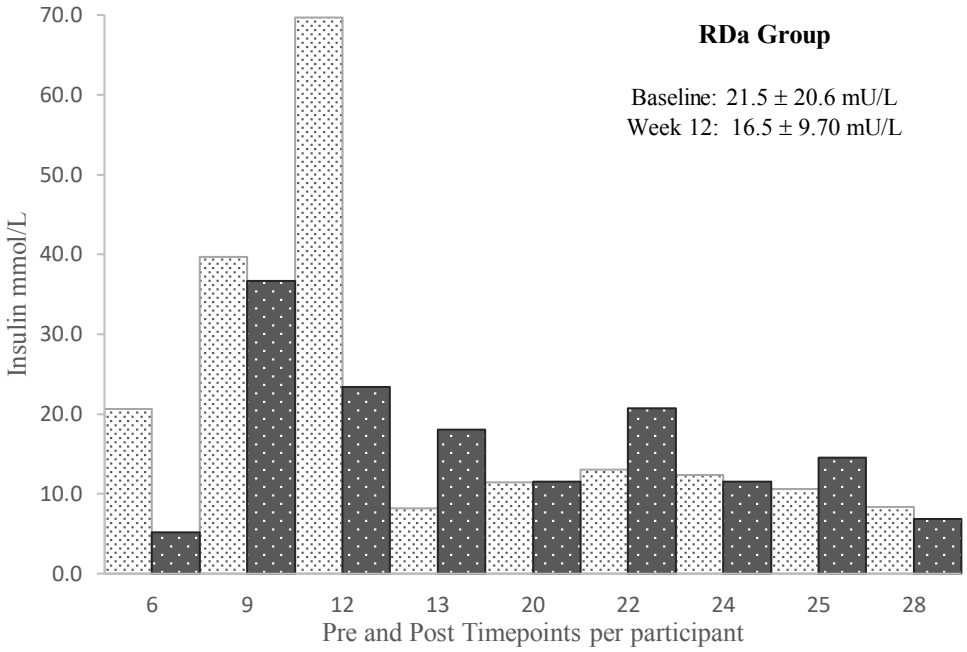

Figure 11. Fasting insulin concentrations at baseline and at week 12 for each participant in the RDa group (numbers in x-axis represent the individual participant numbers). Each bar corresponds to a participant at baseline and at week 12. Baseline in light bars and post-study in dark bars.

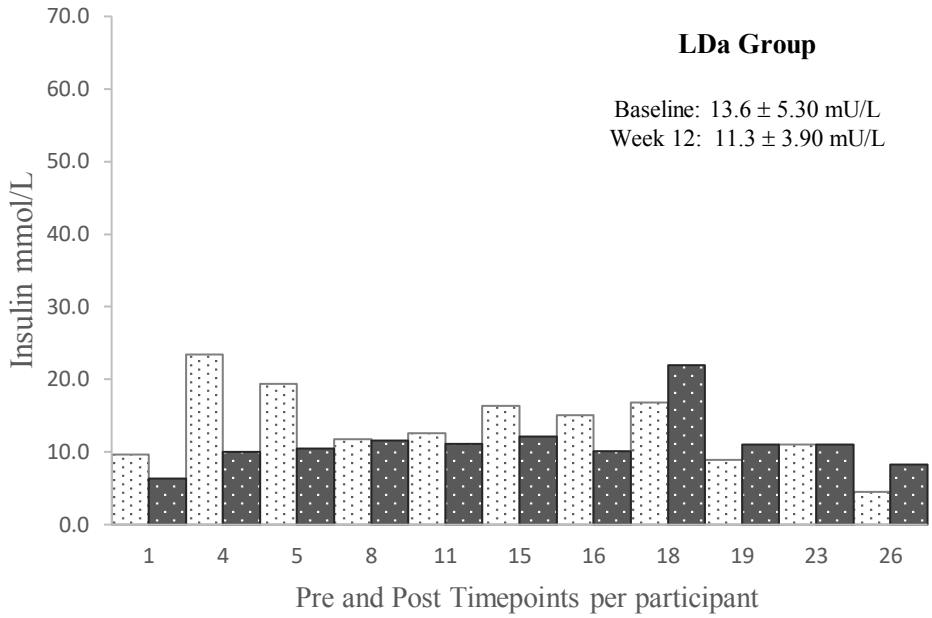

Figure 12. Fasting insulin concentrations at baseline and at week 12 for each participant in the LDa group (numbers in x-axis represent the individual participant numbers). Each bar corresponds to a participant at baseline and at week 12. Baseline in light bars and post-study in dark bars.

Of the 9 participants in the RDa group, 3 increased their fasting insulin levels after the 12-week trial, 1 remained the same and 5 decreased their concentrations (Figure 9). The fact that 5 participants had their insulin reduced suggests that this study may have affected these adolescents positively. On the other hand, the 3 participants that increased their post-study insulin levels were most likely not following the study recommendations, particularly with respect to the diet. The participant that increased her insulin concentration by 9.90 mU/L (#13 on Figure 9) had a death in the family at week 9 of intervention, which affected her daily routine and dietary pattern until the end of study. Her food choices were not in line with the recommendations of the study (i.e. she was consuming more fast-food, cookies and pastries than we would have liked). She was still consuming the 4 servings of dairy per day that the study provided (~1365mg of calcium/day), however she had trouble restricting other foods and

compensating for the increased calories from dairy. She started the study consuming 1774 kcal/day and ended the study consuming 2587 kcal/day. Despite the increased energy intake, this participant improved her body composition by week 12, with a decrease of 1kg of FM and an increase of 2.4kg of LM. The participant whose insulin increased by 7.70 mU/L (#22 on Figure 9) was a first-year university student living on campus. In week 8 of study she started her final exams and was highly stressed. She did not focus as much on eating a healthy and balanced diet as the dietitian and study staff recommended. She was consistently eating the dairy (1380 mg of calcium/day). Based on her food diaries, overall, she was eating a healthier diet by end of study compared to baseline, however she still consumed fast-food and pastries. This participant did not change her body composition by the end of the intervention. Finally, the participant whose insulin increased by 3.95 mU/L (#25 on Figure 9) started working part-time in a fast food restaurant after school and on weekends. She was not as focused on the study by the end (due to her busy schedule) and was making poor food choices. Because she was working in a fast-food restaurant she was consuming these foods more often. Her dairy intake was maintained during the intervention (~1315 mg of calcium/day). She started the intervention with a mean energy intake of 1782 kcal/day and ended the study with 2022kcal/d. Nonetheless, she improved her body composition, with a decrease of 2.4 kg in FM and an increase of 5kg in LM. Despite our best efforts to track and monitor our participants' diets (and facilitate exercise compliance), some participants still may not adhere to the study protocol as well as we would like. On the other hand, the participant who had a decrease of 46.3 mU/L in insulin (#12 on Figure 9) was following the study guidelines very well. At baseline, she was consuming an average of 2000kcal/day and by week 12 she had a self-induced decrease of 400kcal/day, still incorporating the

dairy appropriately (~1365 mg of calcium/day). She decreased FM by 4 kg and decreased LM by of 3.2 kg. This corresponds to a weight loss of 7kg. Although weight loss of this magnitude was not intended to occur in the study, it could greatly improve fasting insulin levels. Nonetheless, the high variability in insulin concentrations affected the total group mean and the standard deviation, which had an impact on the statistical analysis with such small subject numbers.

Of the 11 adolescents in the LDa group, 6 reduced their insulin concentration, 2 remained the same and 3 increased (Figure 10). When examining the data of the two groups together, the LDa and RDa groups followed the same trend, most participants decreased their insulin levels after the intervention (n=11), a few had a neutral effect (n=3) and some had increased their levels (n=6). In the total sample, of the 11 participants that decreased insulin levels, 9 lost FM by an average of -2.4 kg and two participants increased FM by 0.1 and 0.5 kg. Regarding LM, 8 participants gained LM by an average of 3.6 kg and 3 decreased the LM by 0.1, 0.6 and 3.2 kg. It is important to note that this study was not designed for weight loss, which is a larger driver of metabolic change. But it was designed to achieve a change in body composition, which we observed (albeit not between groups as yet). Therefore, the mean reductions in insulin occurred following a healthy approach to lifestyle change; better quality nutrition changes without a prescribed energy restriction and the incorporation of regular exercise 3x/week.

Regardless of the subtle individual differences, the groups overall did not statistically differ between each other. It is possible that the study was not long enough to detect significant changes in fasting insulin levels with lifestyle change, as was seen in the Ho et al. meta-analysis (78), or that the results are attenuated since our study was not designed for weight loss which can independently improve insulin (and

other metabolic variables) (216). For example, a study by Luo et al. demonstrated that an intense 6-week hypocaloric diet and exercise intervention can significantly improve fasting insulin concentrations ($p<0.05$) in OB boys and girls (11-13 years). These children performed a high volume of exercise 6 days/week (twice daily, for 3h each), and were consuming a hypocaloric diet, where 3 meals per day were provided (no emphasis on dairy). Insulin levels improved in as little as 6 weeks in OB Chinese children, but this intervention was much more controlled and rigorous compared to our study, which was not calorie-restricted, included a more realistic prescription of exercise, and included the increased intake of dairy in a real-life environment. In addition, studies that found significant changes in fasting insulin also had larger sample sizes. The study by Luo et al. included 215 children, with 167 participants in the intervention group. The meta-analyses by Ho et al. included 372 (88) and 519 (3) OW/OB children and adolescents (<18 years). It is likely that a larger sample size will provide greater power to detect differences between groups.

Regarding fasting glucose levels, there was no difference between groups or pre-to post intervention. Participants' blood glucose levels were within the normal range at baseline, which likely contributed to the absence of change post-intervention. Our findings supported the meta-analysis by Ho et al., who did not see changes in fasting glucose concentrations (88), as well as the study by Reinehr et al. who found that after 1-year of a lifestyle intervention involving physical activity, nutritional education and behavioural therapy in OB youth (10-16 years), fasting glucose concentrations did not change significantly (2).

5.2 Insulin Sensitivity & Resistance

In our study, average HOMA-IR and QUICKI changes were not significant from pre- to post-intervention or between groups. HOMA-IR and QUICKI are derived from calculations involving fasting insulin and fasting glucose. Therefore, it is unlikely that these measurements would change since mean insulin and glucose concentrations did not change significantly in this study. Nonetheless, when assessing the results of the individual participants, the prevalence of insulin resistance did decrease from 35% at baseline (7 adolescents, 3 in RDa and 4 in LDa) to 25% at week 12 (5 adolescents, 4 in RDa and 1 in LDa). The reduction in insulin resistance occurred mostly in the adolescents from the LDa group. It is possible that we did not see a greater decrease in insulin resistance in the RDa, or the same trend as seen in LDa group because the RDa girls started the intervention with higher body fat/weight compared to the LDa girls. As well, weight loss, which is usually associated with improved insulin levels, was not the focus of this study. However, body fat did decrease, but this decrease may not have been large enough to appreciably affect insulin levels.

There were significant correlations between change in HOMA-IR and change in body mass ($r = 0.53$; $p = 0.02$, Figure 11), and waist circumference ($r = 0.46$; $p = 0.04$, Figure 12) when study participants were combined into one intervention group (n=20). These correlations suggest that a global decrease in adiposity is associated with a decrease in insulin resistance. Similar to our findings, Ling et al. investigated the potential predictors of high fasting insulin and insulin resistance (as HOMA-IR) in 173 OW/OB Asian adolescents, using waist circumference measures, bioelectrical impedance analysis (BIA) and the Modified Harvard Step Test (MHST) (190). They assessed blood lipids, fasting insulin, HOMA-IR, waist circumference, %BF and

physical fitness scores in these youths. They found that BMI had the highest, statistically significant, positive correlation with fasting insulin ($r = 0.51$, $p < 0.0001$) and HOMA-IR ($r = 0.48$, $p < 0.0001$). They also found a positive significant correlation between %BF and fasting insulin ($r = 0.34$, $p < 0.0001$) and HOMA-IR ($r = 0.32$, $p < 0.0001$), as well as positive correlations for waist circumference with fasting insulin ($r = 0.41$, $p < 0.0001$) and HOMA-IR ($r = 0.39$, $p < 0.0001$), and waist:height ratio with fasting insulin ($r = 0.35$, $p < 0.0001$) and HOMA-IR ($r = 0.34$, $p < 0.0001$) (190). Therefore, these findings from Ling et al. along with ours, indicate that a greater body fat/weight is associated with higher plasma insulin concentrations and insulin resistance in OW and OB adolescents. Despite similar findings, there are some critical differences between the Ling study and ours. First, Ling et al is a cross sectional study, whereas ours is a RCT. Second, Ling et al correlated absolute values for these variables, whereas we correlated change values. For these reasons, even with a smaller number of subjects, our study may present stronger findings due to study design differences.

5.3 Lipids

From a subset of 20 participants, the current study showed no significant improvements in TC, LDL-c, HDL-c and TGs after the intervention. Our findings are generally in contrast with the meta-analysis of Ho et al., which observed improvements in TC and TGs in intervention studies up to 2 years in duration, and in LDL-c in intervention studies that lasted 4-12 months. But like us, there was no change in HDL-c (88). The authors indicated that the improvements in serum lipids were possibly due to the improvements observed in aspects of the lifestyle

intervention such as increased physical activity or dietary improvements, as well as the effect of fat loss (88).

In our study, the mean HDL-c concentration (0.96 ± 0.33 mmol/L) was below the normal cut-off at baseline, and the mean for TGs concentration (1.62 ± 0.86 mmol/L) was above the normal cut-off in the RDa group This may be explained by their greater baseline body mass/FM in this group, suggesting a greater risk for CVD in these adolescents. After the intervention, there were minimal improvements in these markers in the RDa group (HDL-c Δ = 0.01 ± 0.22 mmol/L and TGs Δ = -0.07 ± 0.64 mmol/L), with no negative changes. The LDa group had all lipid variables within normal ranges at baseline, except for TGs levels which were just above the normal cut-off (1.14 ± 0.43 mmol/L), by week 12 there was a reduction of -0.23 ± 0.29 mmol/L in TGs in the LDa group. Despite body mass, waist circumference and body composition being greater at baseline in the RDa group *vs* the LDa group, this difference did not affect the response to the intervention in the cardiometabolic variables between groups. That is, the improvements in metabolic variables in the RDa group were not larger than in the LDa group, in fact, we observed the opposite in these participants. It is possible that we saw an attenuated decrease in TGs concentration in the RDa group compared to the LDa group because the RDa group was consuming a higher amount of added sugar from the dairy products provided by the study (14g from 1 cup of chocolate milk and 16g from 2 containers of yogurt, per day). When sugar is ingested, plasma insulin is increased, which activates lipoprotein lipase and inhibits hormone-sensitive lipase. This effect leads to increased lipogenesis and inhibition of lipolysis, which can subsequently increase circulating TGs and lipoproteins, and promote the storage TGs in the adipose tissue and liver (62).

Although different than the current study design, Chen et al. examined the effects of a 2-week residential program with daily aerobic exercise (2 – 2.5h/d) along with a high fibre, low-fat diet where food was provided *ad libitum* to 16 OW youths (10-17 years) (11). After the 2-week, rigorous diet and exercise program, the participants presented significant reductions in BMI, waist circumference and %BF ($p < 0.01$ for all), with improvements in serum lipids (>20% decrease in TC, LDL and TGs, $p < 0.01$ for all), apart from HDL-c that remained the same. Fasting insulin concentration also decreased significantly (32.6%, $p < 0.01$). Similarly, Luo et al. presented significant decreases for TGs, LDL-c, TC and fasting insulin ($p < 0.05$) in boys and girls, except for fasting blood glucose in boys ($p = 0.09$), compared to controls, after 6 weeks of a program involving high volume aerobic exercise (6 days/week, twice daily, for 3h each session) and a low calorie diet (1600-2000 kcal/day) in 167 OB Chinese children aged 11 to 13 years (9).

Therefore, the absence of significant changes in blood lipids in our study may be explained by a few reasons: 1) the small number of participants analyzed for this thesis may have contributed to lower statistical power in the lipid analyses; 2) most adolescents presented normal values at baseline for most blood lipid markers, which may contribute to less room for improvement; 3) the study was not designed for weight loss. Therefore, it is not surprising that we did not see large changes in blood lipids. However, it is important to note that we did not see any significant increases, not even with the addition of 4 svgs/d of dairy products to the diet (which added an additional 27 g of total fat, 17 g of saturated fat and 30 g of sugar); 4) the intensity of the intervention regarding the diet and exercise design was not as strong as other cited studies where positive changes were observed. Possibly, if the current study had implemented a weight loss diet and/or more than 3x/week of structured exercise, we

would have seen significant positive changes in blood lipids. Additionally, it is worth noting that the diet for both the Chen et al. and Luo et al. studies was highly controlled, with all the meals provided for participants (9,11). In contrast, our study employed a lifestyle modification-based diet which reflected normal life situations, with standard dietary counselling by a dietitian and a commonly prescribed schedule of exercise. Thus, the environment was not as controlled (to help mimic real-life). We see this as a critical, intentional feature of our study that will make the results more translatable to the public. With that said, we did monitor our participants well by maintaining constant communication with them, and recording ample amounts of information, such as FRs, exercise plans, step logs and goal setting, frequently.

5.4 Anthropometric and Body Composition Changes

Reinehr and colleagues investigated the effects of a 1-year lifestyle modification program (exercise, nutritional education and behaviour therapy) and the prevalence of MetS in 288 OB children (mean age 12.5 years) (2). Their findings suggest that the improvement of MetS components was correlated with the degree of weight loss in the program. In particular, they found that in a subgroup of children who improved their standard deviation score BMI (SDS-BMI) by 0.5, they showed improvements in all components of the MetS (TGs, HDL-c, blood pressure, fasting glucose, impaired glucose tolerance and waist circumference). Also, children with a minimal weight reduction (<0.25 of SDS-BMI) presented with better glucose tolerance and blood pressure levels (2). Children that participated in the lifestyle modification program that did not reduce body mass, did not improve any of the metabolic variables (apart from a minimal reduction in blood pressure). Thus, the

authors concluded that the amount of body mass reduction is a predictive factor for the improvement of MetS components (2). Other studies support this by also indicating that a reduction of ≥0.25 in BMI z-score is needed for minimal improvement in metabolic markers among OB adolescents (217) and that a decrease of ≥0.5 units is needed for greater improvements (2,217).

The current study did not present significant changes in BMI after the 12-week lifestyle intervention program. Although, a positive change in BMI was observed; it is important to note that, currently, the analyses are likely underpowered to detect a significant change. Moreover, the study was not designed to greatly affect BMI or body mass (only body composition). It is possible that this study would have demonstrated decreases in cardiometabolic factors if the participants had decreased their BMI. The diets prescribed by the dietitian in this study were designed for weight maintenance which could still promote better weight management and body composition change, but not necessarily weight loss. The main goal of the study was to focus on healthy eating (with and without dairy), along with increased physical activity, which would allow for an increase in energy expenditure, affecting energy balance, and in turn decreasing body fat (with a possible increase in LM). As was expected, reductions in BMI and body mass after the 12-week intervention were not observed, but there were improvements in body composition components. Both intervention groups decreased their waist circumference ($p = 0.003$), %BF ($p < 0.001$) and FM ($p < 0.001$), and increased their LM ($p = 0.01$).

BMI (kg/m^2) is widely used as a measure to evaluate the impact of obesity on cardiometabolic risk factors, but does not always reflect obesity per se, and cannot make the distinction between muscle mass, FM and bone (218). Waist circumference is an anthropometric measure used as an indicator of abdominal obesity, with its

related index in children, the waist:height ratio (63). Waist:height ratio has been used as an easy and accessible measurement to detect central adiposity and is associated with cardiometabolic risk in pediatric populations (218). Waist circumference is included in the calculation and adjustment is made for an individual's size by dividing by their height. This may also be advantageous over BMI and waist to hip ratio in children (63,65,218). It is known that higher central adiposity is associated with a greater risk of cardiometabolic diseases such as T2D and CVD (59,63,64,190). Our findings demonstrate an average decrease in waist circumference (102.9 ± 12.1 to 99.8 ± 11.1 cm, $p = 0.003$) and in waist:height ratio (0.63 ± 0.08 to 0.61 ± 0.07, $p = 0.003$) after the intervention in all study participants, indicating that a weight management, healthy diet, with regular physical activity, is effective in reducing central obesity, which also reduces CVD risk in children and adolescents.

A systematic review of RCTs by Kouvelioti et al. examined the effects of dairy consumption on body size, body composition and bone in children and adolescents (119). From the 11 studies that focused in body composition, only one found a significant increase in LM of OW/OB boys and girls, but no significant decrease in FM was found after replacing the regular consumption of SSB with milk for 16 weeks. Therefore, in a pediatric population, the review found no positive association between dairy intake and improvements of body fat and LM, but presented a beneficial effect of dairy on bone tissue (119). Similarly, a recent 12-month intervention study by Lappe et al. did not find an association between increased dairy consumption (>1200mg calcium/d) and improvements in body fat in 274 OW adolescent girls (219). However, during adolescence, girls need calcium and protein (and other essential micronutrients) for maximizing peak bone mass. Dairy products are very good sources of these nutrients (115,122,220).

Many adolescent girls avoid dairy because they are afraid of gaining weight (130). With our findings, it is demonstrated that the daily consumption of milk, yogurt and cheese for 12 weeks had no negative impact on body mass. This shows that while incorporation of dairy into the diet may not significantly improve body composition in this sample of adolescent girls, it does not appear to be detrimental to body composition, and should be used as a nutritional strategy for youth to increase the nutrient quality of their daily diets. A study by Marette et al. showed that dairy foods, such as yogurt are nutrient-dense, accessible, tasty and satiating for children and adolescents, and can be easily incorporated into diets as snacks (221).

5.5 Strengths & Limitations

This is the first study to investigate the effects of increased dairy combined with a lifestyle modification intervention on cardiometabolic variables in OW/OB adolescent girls. This study was a RCT which is the only type of study able to establish causation in a human population. Furthermore, it affords us the ability to carry out an intervention in a controlled manner (as controlled as possible for a lifestyle intervention study design), to manipulate a particular variable of interest, and explore a specific hypothesis relating to it. Thus, the careful design of our study to manipulate only the consumption of dairy between the groups, with lifestyle modification and behavioural support is a strength.

The collection of 3-day and 7-day FRs were a great asset to the study. These diaries gave us the ability to investigate and measure, in-depth, the nutritional intake and habits of our participants. We were able to assess all the nutrients consumed on an ongoing basis, and use these data to reinforce the diet parameters of the study. In

some respects, the study had high compliance, which was measured based on participants' attendance for the exercise sessions and collection of FRs throughout the study. Out of 36 exercise training sessions, the mean attendance was 32 sessions (89% attendance). For the FRs, compliance was greater than 95% with respect to the consumption (or not for the LDa group) of dairy foods. The high compliance can be explained by the support of the study dietitian, personal trainers, Fitbit device and study staff. The adolescents (and, most often, their parents) had 5 1-hour diet consults with a registered dietitian throughout the study, who gave them important information regarding dietary recommendations, helped them set personal goals (i.e. increase or decrease the consumption of certain foods like fruit and vegetables and chips, respectively) and overcome barriers to achieve these. In addition, the girls had a personal trainer for all exercise sessions during the 12-week intervention, which also gave them support and encouragement to keep active, not only on the exercise session days, but on a regular basis through the logging of steps from their Fitbit device. Beyond the dietitian and the personal trainer, the participants also had support from the study staff that met with them frequently and gave them tools to achieve their goals.

Quality control was also assured by study staff. It was always confirmed whether participants had followed the study guidelines before the data was collected, however, response bias may still be a concern. Working with an adolescent population, while not a study limitation or strength, per se, did pose some difficulties with lifestyle compliance. To facilitate change in this population, there is a heavy reliance on parental support and availability, as well as a strong commitment from the participants to attend the training sessions and follow a healthy diet and routine. Every effort was made by the study team to ensure compliance from all participants,

however, working with a human population will always introduce the potential for non-compliance and response bias. We always did our best to mitigate these factors.

A main limitation of this thesis is the small sample size. Only a subset of the total sample for the IDEAL study (20 participants out of 50 in the intervention), could be used in the analyses. Another limitation, specific to the metabolic variables, was the 'normality' of the baseline blood values of participants. Most adolescents presented with baseline metabolic variables within the normal range, which may have contributed to the lack of change (including reduced statistical power and absence of overt weight loss) after the 12-week intervention. Of note, this is only to be seen as a limitation with respect to the detection of differences post-intervention. We are pleased that these adolescents, despite being classified as OW/OB, do not, for the most part, have abnormal levels of common cardiometabolic disease markers.

Another potential limitation is the duration and intensity of the study. Previous studies that investigated the effectiveness of diet and exercise interventions (without dairy intake) in OW/OB children and adolescents that presented significant changes in blood lipids and glucose metabolism had a duration of 4 months to 2 years (3,5,10,88), or implemented a calorie-restricted diet (3,10,88), or implemented a more rigourous regimen of exercise (9,215). It is possible that the study duration and exercise/nutritional strategy of the current study was not sufficient to detect changes in the metabolic variables.

5.6 Implications and Future Directions

The IDEAL for Adolescents study, within this thesis, has several practical implications. It assessed the difference between two groups in a real-life context by

comparing how adolescent girls normally consume dairy (0-1 serving/d the LDa group) (13) to what the nationally recommended amount is based on Canada's Food Guide (4 svgs/d, the RDa group). So far (in a subset of participants), the outcomes reveal that the increased intake of dairy compared to low intakes has no added benefit or deleterious effect on body composition or the metabolic profile of OW/OB female adolescents. Since a major limitation of this thesis was a relatively small sample size, further analysis should be performed with an increased number of participants so more substantial conclusions can be made with adequate power. In addition, a longer study duration may allow us to obtain better quality results. It may be possible that some physiological changes, such as insulin and glucose, may take longer to become apparent than this study allowed. Studies that used a lifestyle intervention approach, with implementation of regular physical activity and a hypoenergetic diet, with longer duration showed significant improvements in cardiometabolic variables and body composition in pediatrics (3,10,88). It would also be interesting to include male adolescents and investigate the effects of increased dairy with regular physical activity on cardiometabolic variables in this population and compare to the female adolescents. Lastly, the use of an energy restricted diet combined with regular exercise for OW/OB adolescents, instead of a weight management design may yield better cardiometabolic outcomes, including intentional weight loss. In addition, it may be beneficial to combine an energy-restricted diet with varied servings of dairy in an attempt to find an optimal dietary strategy to improve cardiometabolic health in OW/OB adolescent girls.

5.7 Conclusion

This thesis investigated the effects of increased dairy consumption combined with exercise and healthy eating on cardiometabolic variables in OW/OB adolescent girls over 12 weeks. From a subset of 20 participants, the analyses in this thesis did not reveal any significant metabolic profile changes, and no differences were seen between the two intervention (LDa and RDa) groups. On the other hand, significant improvements were observed pre-to post-intervention in waist circumference, FM and LM of all study participants (main time effects). Improvements in body composition can be attributed to the lifestyle intervention that included exercise and the consumption of a healthy diet. Dairy did not seem to further amplify these positive effects in the RDa group. In addition, it is important to note that the increased dairy consumption did not show any negative changes regarding cardiometabolic variables or body composition components. The lack of significant improvements in the metabolic variables in both groups is likely due to the absence of energy restriction to produce intentional weight loss and/or the shorter duration of the study. Thus, to attain clinically significant improvements in blood lipids and other metabolic markers, the intervention should have included a larger sample with baseline characteristics of participants without significant differences, had implemented a restriction of calories to induce intentional weight loss, and implemented a longer duration trial of at least 16 weeks to 6 months. Despite the lack of change, the girls consuming dairy did improve their intakes of key nutrients, such as calcium and vitamin D, which contributes to a higher diet quality. Further analysis with a larger sample size is required to determine the true effect of a lifestyle intervention with and without dairy on OW/OB pediatric populations.

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APPENDICES

Appendix A – Ethics Clearance

Brock University
Research Ethics Office
Tel: 905-688-5550 ext. 3035
Email: reb@brocku.ca

Bioscience Research Ethics Board

Certificate of Ethics Clearance for Human Participant Research

DATE: 7/17/2015

PRINCIPAL INVESTIGATOR: JOSSE, Andrea - Kinesiology

CO-INVESTIGATORS: Nota Klentrou, Bareket Falk, Wendy Ward, Sandra Sacco

FILE: 14-284 - JOSSE

TYPE: Faculty Research STUDENT: Rozalia Kouvelioti

TITLE: Effects of a weight management intervention with increased dairy intake on body composition and bone health in overweight and obese girls

ETHICS CLEARANCE GRANTED

Type of Clearance: NEW Expiry Date: 7/29/2016

The Brock University Bioscience Research Ethics Board has reviewed the above named research proposal and considers the procedures, as described by the applicant, to conform to the University's ethical standards and the Tri-Council Policy Statement. Clearance granted from **7/17/2015** to **7/29/2016**.

The Tri-Council Policy Statement requires that ongoing research be monitored by, at a minimum, an annual report. Should your project extend beyond the expiry date, you are required to submit a Renewal form before 7/29/2016. Continued clearance is contingent on timely submission of reports.

To comply with the Tri-Council Policy Statement, you must also submit a final report upon completion of your project. All report forms can be found on the Research Ethics web page at http://www.brocku.ca/research/policies-and-forms/research-forms.

In addition, throughout your research, you must report promptly to the REB:

a) Changes increasing the risk to the participant(s) and/or affecting significantly the conduct of the study;
b) All adverse and/or unanticipated experiences or events that may have real or potential unfavourable implications for participants;
c) New information that may adversely affect the safety of the participants or the conduct of the study;
d) Any changes in your source of funding or new funding to a previously unfunded project.

We wish you success with your research.

Approved:

Brian Roy, Chair
Bioscience Research Ethics Board

Note: Brock University is accountable for the research carried out in its own jurisdiction or under its auspices and may refuse certain research even though the REB has found it ethically acceptable.

If research participants are in the care of a health facility, at a school, or other institution or community organization, it is the responsibility of the Principal Investigator to ensure that the ethical guidelines and clearance of those facilities or institutions are obtained and filed with the REB prior to the initiation of research at that site.