Consumption of added sugars and development of metabolic syndrome components among a sample of youth at risk of obesity

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ABSTRACT

Previous evidence showed controversial links between added sugar intake, diet quality and increasing prevalence of metabolic syndrome (MetS) components (abdominal adiposity, dysglycemia, elevated blood pressure, reduced high–density lipoprotein cholesterol (HDL–C) and hypertriglyceridemia) in youth, and most studied only its liquid source of sugar–sweetened beverages (SSB). To better understand the extent of the detrimental effects of added sugars from both liquid and solid sources to diets in terms of nutrient and food intake and metabolic consequences in children, three studies were undertaken to (i) quantify the associations of added sugar intake with overall diet quality and adiposity indicators; (ii) assess whether excess weight and glucose tolerance status modifies the associations between consumption of added sugars and MetS components; and (iii) evaluate whether consumption of added sugars predicts the development of MetS components over time.

Data for these studies were obtained from the QUébec Adiposity and Lifestyle InvesTigation in Youth (QUALITY) cohort. Caucasian children (8 to 10 years at baseline, n = 630) with at least one obese biological parent were recruited from 1,040 Québec primary schools and followed–up 2 years later (n = 564). Dietary intake, including added sugars (liquid vs. solid) and Canadian Healthy Eating Index (HEI-C) was assessed in three 24–hour recalls at baseline. Adiposity indicators included measured height and weight for body mass index (BMI), BMI *Z*–score, waist circumference (WC), and fat mass (by dual–energy X–ray absorptiometry). Plasma glucose and insulin were measured at fasting and by oral glucose tolerance tests to calculate the homeostasis model assessment of insulin resistance (HOMA–IR) and the Matsuda IS index (Matsuda–ISI). Systolic blood pressure (SBP), concentration of triglycerides and HDL–C were measured by standard instruments. Multivariate linear regression models were used, adjusting for age, sex, pubertal status (by Tanner stage), energy intake, fat mass and physical activity (by 7–day accelerometer).

The main findings include: (i) higher consumption of added sugars from SSB or solid sources was associated with lower nutrient density and lower HEI-C. Positive associations with adiposity indicators were observed with consumption of added sugars from liquid sources only; (ii) higher SSB consumption was associated with higher HOMA–IR and higher SBP among overweight children (≥ 85th BMI percentile), as well as higher SBP and higher WC among children with impaired glucose tolerance. These associations with metabolic indicators were not observed among children whose BMI was below 85th percentile; (iii) no association with added sugar intake was observed for 2–year changes in adiposity, but higher consumption of added sugars from liquid sources was associated with higher fasting glucose, higher fasting insulin, higher HOMA–IR and lower Matsuda–ISI.

In conclusion, this thesis suggested that consumption of added sugars from both solid and liquid sources was associated with a lower overall diet quality, but only added sugars from liquid sources was associated with adiposity indicators. Cross–sectional links with higher levels of SSB intake and MetS components were more evident among overweight/obese and glucose–intolerant children. Consumption of added sugars from liquid sources was not associated with changes in adiposity over 2 years, but was clearly associated with development of impaired glucose homeostasis and insulin resistance. This thesis presents further evidence on the nutritional and metabolic consequences of consuming added sugar from liquid and solid sources.

RÉSUMÉ

Les preuves antérieures ont montré des liens controversés entre la consommation de sucre ajouté, la qualité du régime alimentaire et l'augmentation de la prévalence du syndrome métabolique (SM) composants (adiposité abdominale, dysglycémie, pression artérielle élevée, cholestérol des lipoprotéines de haute densité réduite (HDL-C) et l'hypertriglycéridémie) chez les jeunes, et plus étudié que sa source liquide de boissons sucrées. Afin de mieux comprendre l'impact de la consommation de sucres ajoutés sur l'alimentation des enfants tant en termes des apports alimentaires que des apports nutritionnels, ainsi que les conséquences métaboliques de cette consommation, une série d'études ont été réalisées. Les objectifs de ces études visaient tout d'abord à quantifier les associations entre la consommation de sucres ajoutés (sources liquides et solides) et la qualité du régime alimentaire global de même que les indicateurs d'adiposité, ensuite à déterminer si l'excès de poids et l'état de la tolérance au glucose modifient les associations entre la consommation de sucres ajoutés et les composantes du SM, et finalement, à déterminer si la consommation de sucres ajoutés prédit l'apparition des composantes du SM.

Les données utilisées dans les présentes études proviennent de l'étude de cohorte QUébec Adiposity and Lifestyle InvesTigation in Youth (QUALITY). Dans le cadre de cette étude QUALITY, des enfants de race blanche, âgés de 8 à 10 ans (n = 630) et ayant au moins un parent biologique obèses ont été recrutés (n = 564). Les données ont été colligées à l'entrée à l'étude et au suivi de deux ans. L'apport alimentaire, y compris les sucres ajoutés (liquide ou solide) et l'indice canadien de la saine alimentation (HEI-C) a été évaluée dans trois rappels de 24 heures au départ.Les indicateurs d'obésité incluaient la hauteur et le poids mesurés pour le calcul de l'indice de masse corporelle (IMC), l'IMC Z–score, le tour de taille (TT) et la masse grasse (absorptiométrie bi–énergique à rayons X). Les taux de glucose plasmatique et d'insuline à jeun ont été mesurés ainsi que des tests de tolérance au glucose par voie orale pour le calcul de l'évaluation du modèle d'homéostasie de résistance à l'insuline (HOMA–IR) et de l'indice de Matsuda (Matsuda–ISI). En

outre, la pression artérielle systolique, la concentration plasmatique de triglycérides et les taux des HDL–C ont été mesurés à l'aide de méthodes standardisées. Des modèles de régression linéaires multivariés ont été utilisés, ajustement pour l'âge, le sexe, le stade pubertaire (stade de Tanner), la consommation d'énergie, la masse grasse et l'activité physique (accéléromètre 7 jours).

Les principales conclusions sont les suivantes augmentation de la consommation de sucres ajoutés provenant de sources boissons sucrées ou solide a été associée à la densité nutritionnelle plus en plus bas HEI-C. Les indicateurs d'adiposité ont été positivement associés à la consommation de sucres ajoutés liquides. Une plus grande consommation de boissons sucrés a été associé à plus HOMA–IR et plus la pression artérielle systolique chez les enfants en surpoids, ainsi que plus la pression artérielle systolique et plus TT chez les enfants présentant une intolérance au glucose. Ces associations avec des indicateurs métaboliques n'ont pas été observés chez les enfants de poids normal. Aucune association avec la consommation de sucre ajouté a été observé des changements dans l'adiposité, mais la consommation élevée de sucres ajoutés provenant de sources liquides a été associé à une glycémie à jeun supérieure, l'insuline à jeun élevée, supérieur HOMA–IR et inférieur Matsuda–ISI.

En conclusion, cette thèse a suggéré que la consommation de sucres ajoutés provenant de sources à la fois solides et liquides a été associée à une qualité globale de l'alimentation inférieure, mais seulement sucres ajoutés provenant de sources liquides a été associée à des indicateurs de l'adiposité. Liens transversaux avec des niveaux élevés de consommation boissons sucrées et les composants du syndrome métabolique étaient plus évidents chez les enfants en surpoids / obèses et intolérants au glucose. La consommation de sucres ajoutés provenant de sources liquides n'a pas été associée à des changements d'adiposité plus de 2 ans, mais il a été clairement associée au développement de l'homéostasie du glucose et de la résistance à l'insuline. Cette thèse présente une preuve supplémentaire sur les

conséquences nutritionnelles et métaboliques de sucre ajouté consommation provenant de sources liquides et solides.

ADVANCE OF SCHOLARLY KNOWLEDGE

1. Original contribution to knowledge

This doctoral dissertation identified both liquid and solid food sources of added sugars in children's daily diet intake and provided further evidence on the influence of added sugar consumption from not only liquid, but also solid sources on overall diet quality and its association with metabolic health among children at risk of obesity. The most novel aspect in the dissertation is Manuscript 3 which is the first longitudinal study in children examining the associations between consumption of added sugars and development of impaired glucose homeostasis and insulin resistance over time.

The main findings in this dissertation included:

- higher consumption of added sugars, either from liquid or solid sources, is associated with an overall lower diet quality in children; and significant positive associations with adiposity indicators were observed in consumption of added sugars from liquid, but not solid sources;
- cross–sectional associations between higher sugar–sweetened beverages (SSB) consumption and metabolic syndrome (MetS) components is more evident in overweight/obese and glucose–intolerant children;
- consumption of added sugars from either liquid or solid sources was not associated with changes in adiposity, but liquid added sugars were identified as a risk factor for the development of impaired glucose homeostasis and insulin resistance over 2 years among youth at risk of obesity.

2. Manuscripts for peer–reviewed scientific journals

Wang JW, Shang L, Light K, O'Loughlin J, Paradis G, Gray–Donald K. Associations of added sugars (solid vs. liquid) consumption with diet quality and adiposity indicators in children at risk of obesity. (Under review at *J Acad Nutr Diet*)

Wang JW, Mark S, Henderson M, O'Loughlin J, Tremblay A, Wortman J, Paradis G, Gray–Donald K. Adiposity and glucose intolerance exacerbate components of metabolic syndrome in children consuming sugar–sweetened beverages: QUALITY cohort study. *Pediatr Obes*. 2013;8(4):284-93.

Wang JW, Light K, Henderson M, O'Loughlin J, Mathieu M-E, Paradis G, Gray–Donald K. Consumption of added sugars from liquid, but not solid sources predicts impaired glucose homeostasis and insulin resistance among youth at risk of obesity: QUALITY cohort (Pending revision by *J Nutr*)

3. Abstracts and conference presentations

Wang JW, Light K, Henderson M, O'Loughlin J, Paradis G, Gray–Donald K. Consumption of added sugars from liquid, but not solid sources predicts higher glucose and insulin resistance among schoolchildren: QUALITY cohort. *Appl. Physiol. Nutr. Metab* 2013 (Oral presentation at CNS–SCN 2013 Annual Meeting, May 30 – June 2, Québec city, Canada)

Wang JW, Light K, Johnson–Down L, St–Arnaud–McKenzie D, O'Loughlin J, Paradis G, Gray–Donald K. Liquid and solid sources of added sugar and their associations with body weight and metabolic syndrome components in children. *FASEB J April 9, 2013 27:126.2* (Oral presentation at Experimental Biology 2013, Apr 20 – 24, Boston, USA)

Wang JW, Shang L, Johnson–Down L, St–Arnaud–McKenzie D, Paradis G, Gray–Donald K. Contribution of flavored milk on dietary intakes and its association with body mass index percentile in children at high risk of overweight. *FASEB J* 2012 26:lb389 (Poster presentation at Experimental Biology 2012, Apr 21 – 25, San Diego, USA)

Wang JW, St–Arnaud–McKenzie D, Johnson–Down L, Shang L, Lambert M, Paradis G, Gray–Donald K. Contribution of flavored milk to the positive and

negative aspects of children's dietary nutrition. *Appl. Physiol. Nutr. Metab*. 2012 (Poster presentation at CNS–SCN 2012 Annual Meeting, May 23–26, Vancouver, Canada)

CONTRIBUTIONS OF AUTHORS TO MANUSCRIPTS

This dissertation involves cooperation with a group of authors in the QUébec Adiposity and Lifestyle InvesTigation in Youth (QUALITY) multidisciplinary research team. The candidate joined in the QUALITY team in fall 2010 and began attending the monthly PRODIGY meetings and presenting research findings periodically to the group at the Centre de recherché du l'Hopital Ste Justine. As the principal contributor to the dissertation, the candidate proposed the original research ideas for each manuscript and was responsible for the design and performance of the statistical analysis (including all dietary analysis; estimating values of added sugars, creating food groups, data entry and validation, calculation of daily dietary intake and healthy eating index), data interpretation and manuscript writing.

Dr. Katherine Gray–Donald, the candidate's supervisor, is a co–investigator of the QUALITY study and a principal investigator of a grant secured from Canadian Agri–Science Clusters Initiative which funded Manuscript 1 of the dissertation. Dr. Gray–Donald contributed to the development of the concepts and designs, supervision of statistical analysis and data interpretation and critical revision for all manuscripts.

Dr. Gilles Paradis, the candidate's committee member, is a co–principal investigator of the QUALITY study. Dr. Paradis contributed on the data acquisition and interpretation and critical revision for all manuscripts.

Dr. Jennifer O'Loughlin, the candidate's committee member, is one of the principal investigator s of the QUALITY study. Dr. O'Loughlin contributed to the data acquisition and interpretation and critical revision for all manuscripts.

Dr. Melanie Henderson, one of the principal investigators of the QUALITY study, contributed to the data acquisition and interpretation and critical revision for Manuscripts 2 and 3.

Dr. Sean Mark, a former PhD student of Dr. Gray–Donald, is now a co–principal investigator of the QUALITY study. Dr. Mark contributed to the development of the concepts and interpretation and critical revision for the Manuscript 2.

Dr. Angelo Tremblay, one of the principal investigators of the QUALITY study, contributed to the data acquisition and interpretation and critical revision for Manuscript 2.

Dr. Marie–Eve Mathieu, an expert in physical activity in the QUALITY study team, contributed to the data interpretation and critical revision for Manuscript 3.

Dr. Lei Shang, a visiting professor joining in Dr. Gray–Donald's research team for a one–year program, contributed to the data interpretation and critical revision for the Manuscript 1.

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This four–year's study at McGill is just a short period in my whole life, but it is definitely one of the most important periods to enrich myself for now and for future.

DEDICATION

I dedicate this thesis to my dearest parents, WANG Yichuan and YU Guirong. They are the reasons I could be here.

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LIST OF ABBREVIATIONS

AHA: American Heart Association

ANOVA: analysis of variance

ATP: adenosine triphosphate

BMI: body mass index

BP: blood pressure

CDC: Center for Disease Control and Prevention

CNF: Canadian Nutrient File

CSFII: Continuing Survey of Food Intakes of Individuals

CVD: cardiovascular disease

DXA: dual-energy X-ray absorptiometry

DGA: Dietary Guidelines for Americans

DRIs: dietary reference intakes

DV: daily value

EWCFG: Eating Well with Canada's Food Guide

FFQ: food frequency questionnaire

FMI: fat mass index

FM: flavoured milk

GI: glycemic index

GL: glycemic load

HDL-C: high-density lipoprotein cholesterol

HFCS: high fructose corn syrup

HEI: Healthy Eating Index

HEI-C: Canadian Healthy Eating Index

HOMA-IR: homeostasis model assessment of insulin resistance

IFG: impaired fasting glucose

IGT: impaired glucose tolerance

IS: insulin sensitivity

Matsuda-ISI: Matsuda IS index

MetS: metabolic syndrome

NHANES: National Health and Nutrition Examination Survey

OGTT: oral glucose tolerance test

QUALITY: QUébec Adiposity and Lifestyle InvesTigation in Youth

RCT: randomized controlled trial

SBP: systolic blood pressure

SSB: sugar-sweetened beverages

T2DM: type 2 diabetes mellitus

USDA: U.S. Department of Agriculture

WC: waist circumference

CHAPTER 1. INTRODUCTION

1.1 Background and rationale

Childhood obesity has become a major public health concern worldwide. Since the late 1970s, the prevalence of overweight and obesity has risen among children and adolescents in Canada[1]. Based on the data from the 2009 to 2011 Canadian Health Measures Survey, close to one third (31.5%) of Canadian youth (aged 5 to 17 years), an estimated 1.6 million, were classified as overweight (19.8%) or obese (11.7%)[2]. There has been a tripling in the prevalence of childhood obesity coincident with a rising prevalence of metabolic syndrome (MetS) in both youth and adults over the past 3 decades[3–5]. In 2007 to 2009, about one in five (22%) Canadian adults have MetS[6]. Whereas MetS usually occurs later in life, its risk components[7], including abdominal obesity (high waist circumference (WC)), high blood pressure, dysglycemia (high fasting glucose), dyslipidemia (low high–density lipoprotein cholesterol (HDL–C) and high plasma triglycerides), are increasingly identified in adolescents and even children[8, 9].

Excess weight in childhood has been linked to insulin resistance, type 2 diabetes mellitus (T2DM), and hypertension and tracks into adulthood[10–12]. In the U.S. National Health and Nutrition Examination Survey (NHANES, 1999–2002), the prevalence of insulin resistance was 3%, 15% and 52% in normal–weight, overweight and obese adolescents, respectively[13] and the prevalence of MetS was 1.1 and 26.2% among normal–weight and overweight adolescents, respectively[5]. A recent Canadian surveillance study finds that 95% of children newly diagnosed with T2DM are obese[14]. An estimated 0.8% of Canadian youth (aged 6 to 19 years) had elevated blood pressure in 2007 to 2009[15]. The tracking strength of blood pressure from childhood to adulthood increases with body mass index (BMI)[16], and is the strongest in overweight and obese youth[17]. Though MetS among children is rare, an increase in its risk components at younger ages and their apparent tendency to track into adulthood highlights the need for early and effective prevention efforts[18, 19]. In addition, considering the enormous health care costs[20], there is a strong rationale for identification of modifiable diet and lifestyle

factors (i.e., physical activity, which is associated with a reduced risk of MetS components[21, 22]) for prevention of T2DM and cardiovascular diseases (CVD).

A healthy diet is an important component for normal growth in children and adolescents[23]. There are limited data regarding trends in food and nutrient intake in Canadian children due to a lack of consistent data gathered at the national level. The most recent Canadian Community Health Survey (2004) is the first national survey of eating habits since the early 1970s[24]. Among Canadian youth, 60% of children aged 9 to 13 have fewer than 6 daily servings of vegetables and fruits, while 61% of boys and 83% of girls did not meet the recommended minimum of 3 daily servings of milk products[25]. Accordingly, not all children consume essential nutrients in sufficient quantities. For example, the prevalence of inadequate vitamin A, magnesium, zinc, and phosphorus ranges between 10–30%, and even as high as 67% for calcium in Canadian youth aged 9 to 13 years[26]. It is necessary to understand the dietary risk factors during childhood and adolescence so as to provide preventive measures against the rise in the prevalence of obesity and its metabolic consequences[27]. A number of studies have been carried out to develop effective intervention strategies among obese children, but it is still unclear of the most effective intervention in assisting them to improve body composition without affecting growth rates and the foundation for all current treatments comprises modifying lifestyle and limiting energy intake[28]. Longitudinal studies among children did not yet find clear associations between energy intake or diet composition and development of weight gain[29, 30]. Of all the related dietary factors, prospective cohort studies have only found a consistent association between obesity development and sugar–sweetened beverages (SSB) consumption[29].

In recent decades, diet worldwide shows dramatic increases in the consumption of sweeteners[31]. The preference for sweet–tasting foods and beverages likely relates to high consumption of sugars, especially among children and adolescents[32]. One notable change corresponding with the increased incidence of obesity and insulin

resistance is the increase in the consumption of added sugar, mostly in the form of SSB[33, 34]. Although data from the U.S. indicate recent decreases in the consumption of added sugars, the average intake remains high[35]. Youth are the highest consumers of added sugars, among whom children aged 9 to 13 years consumed as high as 419 kilocalories per day[36]. Added sugars are defined as caloric sweeteners added to foods and beverages during processing or preparation, including sugars and syrups added at the table[37]. SSB are the main liquid source of added sugars in youth's diet in both the U.S. and Canada[38, 39], which include the full spectrum of soft drinks, fruit drinks, energy and vitamin water drinks (but not diet drinks, flavored milks or 100% fruit juice)[40]. Flavored milk (FM) is another liquid source of added sugars that is particularly popular among youth at school. In New York City public schools in 2009, chocolate milk accounted for approximately 60% of total milk purchases[41]. The increasing intake of SSB over milk in children's diets has a negative effect on their diet quality[42–44]. However, when sugars are added to nutrient–dense foods, such as sugar–sweetened dairy products (i.e., FM), youths' diet quality tends to improve[43, 45, 46]. In addition, more than 60% of daily added sugar intake comes from solid food[47], and the top sources include grain–based desserts, dairy desserts, candies and ready–to–eat cereals[36]. Studies comparing the impact of added sugars from liquid versus solid foods on subsequent dietary intake have been conducted only in adults to date. One possible mechanism is that dietary compensation is weaker for sugar intake from beverages than for solid food forms of comparable nutrient content[48]. To date, no specific recommendations have been made on an upper cut–off level for the quantity of added sugars for healthy children.

Studies examining the associations between consumption of added sugars and diet quality and MetS components in youth remain inconclusive. There is evidence in some[49, 50] but not all[51–54] studies that higher intake of added sugars reduces micronutrient intake and displaces nutrient–dense foods in youth. Several systematic reviews indicate longitudinal associations between higher intake of added sugars and weight gain in youth[55–57]. However, not all studies in children

and adolescents show such associations[55, 59]. The association between high SSB intake and higher blood pressure is supported by several studies in adults[58–60] and only one in adolescents[61]. Evidence from cross–sectional studies in youth and intervention trials in adults suggest that higher levels of consumption of added sugars, primarily in the form of SSB, are linked to impaired glucose homeostasis and insulin resistance[62–65]. However, these above findings were not evident in all studies[66–68].

There are some limited indications from both animal and human studies that excess adiposity or insulin resistance may modulate the metabolic response to carbohydrate and more specifically to SSB intake[69–71]. However, to date, few studies compared the associations with SSB consumption and metabolic health among overweight/obese children[71, 72] and no study yet examined such association between children with and without impaired glucose tolerance (IGT). In addition, there are no cohort studies in children or adolescents examining longitudinal associations between consumption of added sugars and glucose homeostasis and insulin resistance. Moreover, previous studies relating added sugars to dietary intake and health outcomes generally treat added sugars overall or only in the liquid form (i.e., SSB and/or FM)[37]. Two randomized controlled trials in adults suggest that added sugars from liquid and solid sources have different effects on body weight[73, 74]. Because most of added sugars consumed by youth come from solid sources[47], the importance of examining their role as well as SSB is recognised in a recent statement by the American Heart Association (AHA)[37], based on the summary of previous evidence from both youth and adult populations.

1.2 Statement of purpose

The overall hypothesis of this study is that higher consumption of added sugars, either from liquid or solid sources, is associated with a lower diet quality and a higher risk of MetS components over time in children. The dissertation is composed of 8 Chapters as outlined below:

Chapter 1 introduces the overall background (including the rising prevalence of obesity and MetS component in pediatric population and increasing consumption of added sugars over the past decades) and summarized what is "known" or "unknown" about the relationship between added sugar intake, diet quality and MetS components in youth.

Chapter 2 provides a comprehensive literature review, including background information on added sugar (definition, dietary sources and metabolism) and review of previous evidence (study design, participants, measurements, statistical analysis, strengths and limitations and potential mechanisms).

Chapter 3 provides details of methods for the dissertation (recruitment and measures of participants in the QUébec Adiposity and Lifestyle InvesTigation in Youth (QUALITY) cohort study, overall design of secondary data analysis, estimation of added sugars, calculation of overall dietary data and statistical analyses for all manuscripts).

Chapter 4 is the first manuscript of the dissertation. It describes the distribution of the two sources of added sugars (solid vs. liquid); compares the daily intake of nutrients and foods and the Canadian Healthy Eating Index (HEI–C) score among tertiles of solid added sugars, tertiles of SSB and between non–drinkers and FM–drinkers; and examines the cross–sectional associations with several adiposity indicators between consumption of added sugars from solid and liquid sources.

Chapter 5 is the second manuscript of the dissertation. It examines the cross–sectional associations between SSB intake and MetS components among children above and below the 85th BMI percentile and those with and without IGT.

Chapter 6 is the third manuscript of the dissertation. It examines the longitudinal associations between added sugar consumption (solid and liquid sources) and

adiposity, glucose homeostasis and insulin sensitivity (IS) among youth over 2 years.

Chapter 7 serves to link the findings in this dissertation to its practical significance in public health, and summarizes historical progress of dietary guideline referring to identification of added sugar intake, healthy eating and lower risk of MetS components. It also lists the effects of dietary environment changes (home, schools, nearby environment and media) on added sugar consumption and chronic disease prevention particularly in the youth population. Lastly, it summarizes the current policies by governments and actions by industry in regulating added sugar intake (taxation, school nutrition program and reducing added sugar in foods and beverages, etc.).

Chapter 8 summarizes the findings in our study and compares this with previous evidence. It also describes the strengths and limitations of the entire study and proposes directions for future studies.

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CHAPTER 2. LITERATURE REVIEW

2.1 Background

During the past 10 years, there has been a sharp rise in the prevalence of overweight and obesity around the world, paralleled with the nutrition transition and lifestyle changes, which increasingly promote positive energy balance[1–3]. This high prevalence does not only exist in adults, but of particular concern is the magnitude of increase occurring among children and adolescents[4]. Based on the data from NHANES, over the past 3 decades, the prevalence of obesity (age– and sex–specific body mass index (BMI) ≥ 95th percentile) has more than doubled across all age groups[5] and is currently 19.6% in those aged 6–11 years and 18.1% in those aged 12–19 years[6]. While in Canada, according to the recent Canadian Health Measures Survey (2009–2011), nearly 31.5% of Canadian youth (5–17 y) were overweight or obese[7]. The implications of excess body weight are far–reaching.

The increasing prevalence of MetS and T2DM in the pediatric population is a global health issue[8–10]. MetS comprises a cluster of risk factors for CVD which includes central obesity, dyslipidemia (higher triglyceride, decreased HDL–C), hyperglycaemia (higher fasting plasma glucose) and hypertension (elevated blood pressure)[11]. According to the data from the NHANES (1988–1994), the prevalence of MetS was 6.8% among overweight adolescents and 28.7% among obese adolescents[12]. The most recent survey data of youth aged 8 to 17 from NHANES indicate that the prevalence of pre–hypertension and hypertension has now reached 10% and nearly 4% respectively[13]. In addition, the prevalence of hyperglycaemia and diabetes is rising globally[14], contributing to a significant increase in morbidity and mortality[15]. Impaired fasting glucose (IFG) and impaired glucose tolerance (IGT) represent intermediate prediabetic conditions in the transition between normal glucose homeostasis and diabetes[16].
Epidemiological studies indicate that obesity is one of the most important risk factors for developing insulin resistance, T2DM and CVD[17, 18], while insulin resistance is found among a large number of overweight adolescents underpins the

pathophysiology of MetS[19]. Although the diagnosis of T2DM is rare among young children, youth are more vulnerable to the development of T2DM at puberty[20]. The rapid progression from normal glucose homeostasis to the development of prediabetes in children and adolescents underscores the need for prevention of T2DM[21].

2.2 Macronutrient intake

A healthy balanced diet helps to promote the normal growth of children, and is benefical in preventing the development of obesity and related chronic metabolic diseases when they grow up[22]. Children's usual nutrient intakes[23] can be used to evaluate the prevalence of excessive or inadequate consumption of certain nutrients by comparing their mean intake levels to reference values in the Dietary Reference Intakes (DRIs), which included the recommended dietary allowance (RDA) and adequate intake (AI)[24].

2.2.1 Protein

Based on the Institute of Medicine DRIs report, there is still insufficient evidence to identify an upper level of protein intake above which harm might occur[25]. Previous evidence shows that modestly increasing the proportion of protein in the diet, while controlling for total energy intake, may help to improve body composition[26, 27]. Comparing with the isoenergetic consumption of carbohydrate or fat, protein is found to be more satiating under most conditions[28–30]. Several review articles have noted that an increased consumption of dietary proteins results in greater body weight loss[31, 32]. Despite the fact that high–protein diets may have beneficial effects on body weight and energy homeostasis, their potential long–term consequences on glycemic control and insulin resistance limit their appeal for improving energy balance[33].

2.2.2 Fat

Fat is an essential substance in foods, which mainly includes triglycerides, fatty acids, phospholipis, and cholesterol[34]. Fat might be the most controversial nutrient studied in the obesity literature. Because of the higher energy content of fats (9

kcal per gram vs. 4 kcal per gram for both protein and carbohydrate), it is reasonable to assume that a higher consumption of fat contributes to greater energy intake. Dietary fat stimulates excess energy intake through its high palatability and lack of satiating power, which is different than protein and carbohydrate[42]. Some evidence shows that individuals who consume a low–fat diet often unintentionally reduce their total energy intake[35]. Hu et al. summarized previous evidence and indicated that a higher intake of polyunsaturated fat and possibly long–chain n–3 fatty acids is beneficial, whereas a higher intake of saturated fat and trans–fat could adversely affect glucose metabolism and insulin resistance[36]. Although fat has been focused as the macronutrient most associated with metabolic health, it has become increasingly clear that the quantity and quality of carbohydrates in the diet may be equally as important as fats to reduce diet–related chronic disease[39, 40].

2.2.3 Carbohydrates

Carbohydrates can also contribute to excess energy intake and subsequent weight gain. Simple carbohydrates include the different forms of sugar (monosaccharides and disaccharides), whereas complex carbohydrates (polysaccharide) include starches and dietary fiber[45]. There is no clear evidence that altering the proportion of total carbohydrate in the diet is an important determinant of energy intake[46]. Although total carbohydrate intake encompasses a wide range of food groups, including grains, cereals, fruits & vegetables and sweets, it appears that foods which are higher in sugar content or those that have a higher glycemic index (GI) tend to be the more controversial carbohydrate contributors to obesity and related chronic diseases[47]. The GI is defined as the incremental area under the two–hour blood glucose response curve (AUC) following a 12–hour fasting and ingestion of a food with a 50 g of carbohydrate from glucose as a reference (GI = 100)[48]. The GI of carbohydrate–containing foods varies substantially, with fructose having a particularly low GI of 20 and glycemic load (GL) is calculated by multiplying the GI by the amount of carbohydrate consumed[49]. Randomized interventions in obese adolescents shows that low–GI diets resulted in significantly lower

adiposity (BMI and total fat mass) and lower values of homeostasis model assessment of insulin resistance (HOMA–IR) than did standard reduced–fat diets[50]. Decreasing intake of fat, however, and increasing intake of energy and carbohydrates have become national trends in a number of affluent nations. This trend has been suggested to led to an increase in carbohydrate–induced hypertriglyceridemia[51].

2.2.3.1 Fructose vs. glucose

Fructose is the sweetest sugar naturally existed[52]. Because of equivalent sweetness to sucrose and low cost, high fructose corn syrup (HFCS) was widely adopted by industry in North America and became the predominant sweetener in processed foods and drinks, particularly in sugar–sweetened beverages (SSB) since 1980s[53]. The metabolism pathway of fructose is completely different from that of glucose[54]. Glucose enters cells by the glucose transporter (GLUT4), which is insulin–dependent in most tissues. Insulin activates its receptor, which will in turn raise the density of glucose transporters on the cell surface. Glucose is phosphorylated by glucokinase to become glucose–6–phosphate when facilitated to enter the cell. Then phosphofructokinase can manage the conversion of glucose–6–phosphate to the glycerol backbone of triacylglycerols[34]. In contrast, fructose enters cells via GLUT–5, which does not depend on insulin. Fructose is phosphorylated to turn into fructose–1–phosphate once entering the cell, which will be further cleaved by aldolase to generate trioses, the backbone for synthesizing phospholipid and triacylglycerol[34]. Fructose also provides carbon atoms for the synthesis of long–chain fatty acids. Therefore, fructose could facilitate the synthesis of triacylglycerols more efficiently than glucose, so it is thought to be more lipogenic than glucose[34].

In addition, the hormonal pattern seen with digestion of fructose which is lack of increased insulin, reduced leptin and attenuated postprandial suppression of ghrelin[55], is the opposite of that seen with glucose[56]. Therefore dietary fructose is expected to stimulate insulin secretion less than glucose and glucose–containing

carbohydrates[52]. Insulin could stimulate leptin release from adipocytes[57] and assist in insulin circulation, thus leptin concentrations will be lower after ingestion of fructose–containing meals compared with consumption of glucose–containing meals, which might inhibit appetite less than consumption of other carbohydrates and therefore lead to an overall increase in energy intake[52]. Leptin generally decreases with fasting, rises with food intake and is thought to decrease appetite[58], while ghrelin acts in the opposite way[56]. Fructose does not stimulate the production of two key hormones, insulin and leptin, which are involved in the long–term regulation of energy homeostasis. Compared with the eucaloric glucose ingestion, fructose favors de novo lipogenesis, which could increase adiposity. Therefore, the decreases in insulin responses to meals and in leptin production that are associated with chronic consumption of diets high in fructose may have deleterious long–term effects on the regulation of energy intake and body adiposity[56].

Furthermore, fructose is unique among carbohydrates because it could also lead to the synthesis of uric acid. This product is due to the fructose phosphorylation by fructokinase, which uses adenosine triphosphate (ATP) as a phosphate donor. Accumulation of fructose–1–phosphate is expected to cause depletion of hepatic ATP and rise in the degradation of nucleotides to uric acid[59]. The resulting dyslipidemia and hyperuricemia facilitate insulin resistance[60], and aggravate hypertension[61]. Fructose–induced hyperuricemia has been regarded as a causal mechanism for the epidemic of the MetS[62].

2.2.3.2 Fibre

Dietary fibers are the structural parts of plants and thus are found in all plant–derived foods, such as fruits, vegetables, whole grains and legumes[63]. Increased intake of fruits and vegetables may provide the best means to increase dietary fiber intake among youth[64]. Higher fibre content contributes to a lower energy density of foods[65]. When dietary fibres pass through the gastrointestinal tract, the bonds between monosaccharides in dietary fiber can not be broken down by

digestive enzymes, therefore they contribute no monosaccharides, and thus little or no energy[66]. They may also decrease energy absorption by lowering the bioavailability of fatty acids and proteins[66].

High–fiber diets are suggested to reduce risk for developing obesity, diabetes, and hypertension[67, 68]. Fiber intake is inversely associated with BMI at all levels of fat intake after adjusting for confounding factors[65]. Fibre–rich foods generally take longer to chew, which may increase sensory satiety and reduce meal size[66]. Particularly, viscous fibres can be fermented in the colon[69] and have been suggested to reduce energy intake through increased feelings of satiety by forming a viscous gel in contact with water[70]. It has been suggested that dietary fibre could delay gastric emptying, which not only contributes to a sensation of fullness[71], but also leads to a more gradual nutrient absorption[46] (including glucose) and thus to a low increase in blood glucose levels and a subsequently decreased insulin secretion[72]. These beneficial effects on blood glucose and insulin concentrations are most evident in individuals who have diabetes mellitus. Observational studies have suggested that dietary fiber intake is inversely related to blood pressure[73]. Some, but not all RCT have identified a blood pressure–lowering effect of dietary fiber intake[74]. Substantially increasing carbohydrate intake while limiting fiber intake clearly increases fasting serum triglyceride values[68]. However, increasing dietary carbohydrate with proportional increases in dietary fiber, especially from whole grain sources, does not significantly affect fasting serum triglyceride values[68].

2.3 Added sugars

The U.S. Department of Agriculture (USDA) defines added sugars as "all sugars (caloric sweeteners) used as ingredients in processed and prepared foods (such as breads, cakes, soft drinks, jam, and ice cream), and sugars eaten separately or added to foods at the table"[75]. Specifically, added sugars include white/brown sugar, raw sugar, corn syrup (including HFCS), malt/maple syrup, fructose sweetener, honey, molasses, and etc[76]. Added sugars do not contain the naturally

occurring sugars lactose (in milk and dairy products) or fructose (in fruit)[75]. More complex carbohydrates — glucose–containing oligo– and polysaccharides — are not considered as added sugars[77]. To date, the latest version of Canadian Nutrient File (CNF, 2010) does not distinguish between natural and added sugars[78].

The consumption of added sugars has increased markedly over the past decades around the world, with beverages being a major contributor[79]. Americans' consumption of added sugars has been estimated using national food consumption survey data and USDA Economic Research Service food availability data[75]. Although in recent years there has been a slight decrease in the consumption of energy–containing sweeteners in the U.S. food supply[80], intakes remain substantially higher than they were 4 decades ago[81, 82]. Between 1970 and 2005, average annual availability of sugars increased by 19%, which added 76 kilocalories to Americans' average daily energy intake[81]. In 2001 to 2004, the usual intake of added sugars for Americans was 355 kilocalories per day and as high as 419 kilocalories per day particularly among youth[83]. Today in the U.S., the most commonly consumed added sugars are refined beet or cane sugar (sucrose) and HFCS[84], all of which contribute fructose and glucose in approximately equal amounts to the diet. Added sugars are estimated to contribute 74% to 80% of the dietary fructose consumed[85, 86]. While the per capita average consumption of refined cane and beet sugars has decreased from 1970–1974 to 2000 by 35%, the consumption of corn sweeteners has increased by 277%, with HFCS increasing by 4,080%[87], which is used extensively in soft drinks, baked goods, condiments, prepared desserts, and other processed foods[54]. Ludwig points out that the effect of consuming refined sugars on glycemic response represents an important negative metabolic health consequences caused by such caloric sweeteners, which is related to increased dietary intake and other metabolic complications[88]. Foods high in added sugars have been proposed to be associated with higher risk of adiposity as compared with starchy foods because of lack of dietary fiber and high energy density[89], higher palatability because they are

sweeter[90], unique effects of fructose[54] and because these are often consumed in the form of high–calorie liquids instead of solid foods[91].

2.3.1 Liquid sources

2.3.1.1 Sugar–sweetened beverages (SSB)

SSB include caloric-sweetened soda/cola/coffee/tea/water, sports/energy drinks, and sweetened fruit or vegetable drinks containing less than 70% of natural fruit or vegetable juice (milk, milk products, milk substitutes, dietary aids, and infant formula are exempt)"[92], which primarily use HFCS as the sweetener and on average contain 140 to 150 kilocalories per 12–oz (355 mL) serving[93]. During the past three decades, the consumption of SSB has been dramatically increased across the globe[55]. For example, in the United States, between the late 1970s and 2006, the per capita consumption of SSB increased from 64.4 to 141.7 kcal/day[79], which has already been identified as the primary source of added sugars in the American diet[75]. Particularly among adolescents, SSB count as a significant source of calories that 65% girls and 74% boys consume daily[94]. Similar trends of increase have been shown in Mexico, with SSB currently accounting for 10% of total energy intake[95]. Food disappearance data at national levels from India, China, Thailand, and some other South Asian countries also show a rapid rise consumption of SSB, which is the truth as well for the large per capita intake across Australia and some European countries (such as Great Britain, Germany, Spain and etc)[96].

Time–trend data in the U.S. over the past 3 decades have shown a close parallel between the obesity epidemic and rising levels of SSB consumption[97]. At the same time, a decrease in energy consumed from milk, has taken place, particularly among children, while juice consumption has remained relatively stable across all age groups[98]. The most recent data from U.S. show that children consume about 172 kcal per day from SSB[99]. It has been estimated that percent of total daily calories from SSBs increased from 4.8% in the late 1970's to 10.3% in 2001 among those aged 2–19 years[100]. Similar to U.S. data, SSB is also ranked as the

top single liquid source of total sugars in Canadian adolescents but almost 60% of the average daily total sugar intake of children and adolescents came from solid sources[101].

2.3.1.2 Flavoured milk (FM)

FM, the most popular milk choice in schools, is available in traditional flavours such as chocolate as well as innovative flavours including strawberry, vanilla, mocha and root beer[102]. FM is a nutrient–dense milk beverage providing the same micronutrients as unflavoured milk, including calcium, potassium, phosphorus, protein, vitamins A, D and B_{12}, riboflavin, and niacin[103]. Despite the important nutrient contributions FM makes to the diet, concerns about the potential effects of the added sugars and flavourings in FM have raised questions regarding the role of FM in a healthy diet. FM contains both natural sugar (12 g of lactose per 236–mL serving, 8–oz) and added sweeteners[104]. Sweeteners can be nutritive (caloric) such as sucrose or HFCS, or artificial (non–caloric), depending on the product brand. But added sugar content in different FM products may vary widely, considering the type of added sweetener(s) and amount is unique in the formula in each manufacturer[103]. On average, a 236–mL serving of low–fat chocolate milk contains about 16 grams of added sugar, while an equivalent volume of soft drink contains 28 grams. A 236–mL serving of low–fat (1%) chocolate milk provides 158 calories, whereas its unflavoured counterpart provides 102 kilocalories[102].

In Canada, the average yearly consumption of chocolate drinks (including chocolate milk and chocolate milk beverages) is about 4.2 litres per person, which translates into 12 mL per day[105]. This represents only 7% of total fluid milk consumption, which is about 58 litres per person, per year[105]. Chocolate milk represents 6% of total milk product consumption[105, 106]. The estimated contribution of added sugar from chocolate milk consumption per person per day is < 1 g/day, or less than 1% of total added sugar intake[23]. Meanwhile, more than one–third of children aged 4 to 9 do not meet the recommended two servings of milk products a day[107].

2.3.2 Solid sources

Based on a recent analysis of dietary sources of added sugars among U.S. youth (2 – 18 y), SSB are the largest contributor of added sugars (173 kcal/d), while the rest came from solid sources, such as grain desserts (40 kcal/d), dairy desserts (29 kcal/d) and candy (25 kcal/d)[108]. The list does not vary markedly by age and demographic group. Among Canadian children (1–8 y), the situation is different. Only 9.8% of total sugars come from SSB (soft drink and juice drinks), while other 49.4% and 40.8% come from other liquid sources (milk and fruit juice) and solid sources (e.g., fruit, confectionary, white/brown sugars, other sugars and cereals), respectively; whereas among adolescents (9–18 y), SSB and other liquid sources (milk and fruit juice) contributed 21.7% and 23.1% of total sugars, and all of the rest (55.2%) derived from solid sources[101].

2.4 Added sugars, diet quality and metabolic health among youth

During the past decades, there is a dramatic increase consumption of dietary sugars, in parallel with a raised prevalence of obesity and cardiovascular disease worldwide, which attracted heated concerns about the adverse effects of excessive sugar intake. Previous evidence exploring the relationship between added sugar intake and health outcomes found that higher intakes were associated with greater energy intake, lower intake of other nutrients[109], decreased diet quality[109–111], higher body weight[92, 112–116] and worse health indices (i.e., T2DM[96, 113, 117, 118, 104–106] and MetS[117, 119]) in both youth and adults. Trials have documented that limiting soft drink consumption has a modest beneficial effect on weight in children[120, 121]. Although most studies reported positive associations, some produced inconsistent results, which adds controversy in this field[122].

2.4.1 Added sugars and diet quality

Over the years, several measures have been developed to evaluate diet quality from as many as four aspects: adequacy (measure of sufficiency), moderation (whether certain nutrients or foods are consumed in excess), variety (diversity of

food choices) and balance (the equilibrium of food choices)[123]. The Healthy Eating Index (HEI) is one of the most widely applied measures. Because dietary recommendations in Canada and the United States are similar, the American HEI has been adapted to the Canadian situation[123–125]. Recommendations are expressed as number of servings, according to age and sex, as specified in the *Eating Well with Canada's Food Guide* (EWCFG)[126]. One of the advantages of using the American HEI as a basis for constructing a Canadian index is that its validity of content and construct has been evaluated[127]. Content validity is the degree to which the components of HEI captures the key concepts of the EWCFG, while construct validity refers to the menus developed by nutrition experts, such as National Heart Lung and Blood Institute's *DASH Eating Plan*[128], Harvard's *Healthy Eating Pyramid*[129] and the AHA's *No–Fad Diet*[130].

2.4.1.1 Total added sugars

A study of 4–day food records from 2,206 Norwegian youth (4–13 y) reported that negative associations were observed between added sugars and intakes of micronutrients, fruits and vegetables (30 – 40% lower)[131] (Table 2.1). Alexy et al., analyzed 3–day weighed dietary records from 849 German youth (2–18 y) and found that added sugar intake (average as 12.4% of total energy) was positively associated with intake of total energy, while negatively associated with most micronutrients and nutrient–bearing food groups[132]. Joyce et al., examined 7–day food records among 1,035 Irish youth (5–17 y) and reported that high consumption of added sugars was associated with a decrease in micronutrient density (magnesium, calcium, zinc, vitamins B_{12} and C) of the diet and increased prevalence of dietary inadequacies[133]. An analysis of 3–day food records from 405 British children aged 11–14 years found that those eating the highest amount of added sugars (adjusted for energy intake) consumed less protein and vitamin D compared with those who ate the lowest amounts of added sugars, which suggests that consuming diets lower in added sugars were associated with a more nutrient–dense diet[134]. Although some differences in the nutrient intakes of the high and low added sugar groups were observed for girls only, non–significant trends were

observed in both sexes. However, when added sugar intake was expressed as absolute weight (grams), intake of energy and most nutrients were considerably higher in those consuming high levels of added sugars, probably because of their higher intake of foods in general. Lyhne et al. examined 7–day food records in 983 Danish youth (4–14 y)[136] and reported a significant decline in nutrient density for all nutrients, except vitamin C, as quintiles of added sugar concentration (ranging from 3.4% to 38% of energy intake) rose. The nutrient densities expressed relative to recommended values varied from 30% to 300%, illustrating that the nutritional significance of the dilution effect of added sugars differs from one nutrient to another. Kranz et al., examined the Continuing Survey of Food Intakes of Individuals (CSFII) (1994 –96, 1998) data among a sample of 5,437 U.S. preschoolers (2 – 5 y) by comparing the dietary intakes between 5 categories of % energy from added sugars (≤ 10% to > 25%) and found that increasing added sugar consumption was paralleled by decreasing nutrient and food intakes and increasing proportions of children with intakes below the DRIs[141]. Especially, calcium intake was insufficient in large proportions of children consuming energy of 16% or more from added sugar. Also using the dataset from CSFII (1994–96), Forshee et al. assessed the statistical and practical significance of added sugar intake for nutrient adequacy in U.S. youth (6–19 y) and found that those who had higher added sugar consumption was predicted to consume more grains, vitamin C, iron, folate, but less dairy and fruit[138]. The authors suggested that all the associations, either positive or negative, were small from either a practical significance or in comparison to the association with energy from other sources. However, energy intake was not adjusted in this study, which has been regarded as an essential confounder to explore the true associations, especially considering the wide age range in the participants[148].

2.4.1.2 Sugar–sweetened beverages

Besides research on added sugars as a whole, there were also a number of studies examining the contribution of added sugars especially from SSB and/or FM to

Table 2.1 Evidence of associations between added sugar consumption, nutrient/food intake and weight status in children and adolescents

Reference	Participants	Methods	Findings
Rugg–Gunn AJ, et al., 1991[134]	• British children • 11 – 14 y • n = 405	• 3–day food record • 30 subjects with the highest intake of added sugars vs. 30 with the lowest intake of added sugars	• highest ***added sugar*** consumer had <u>less</u> intake of **protein** and **vitamin D** • Consuming diets containing <u>low</u> levels of ***added sugars*** provided a more **nutrient–dense diet**
Harnack L, et al., 1999[135]	• U.S. youth • 2 – 18 y • n = 1,810	• two 24–hour recalls	***SSB*** consumption • <u>positively</u> associated with **energy** intake • <u>negatively</u> associated with **milk** and **fruit juice**
Lyhne N, et al., 1999[136]	• Danish youth • 4 – 14 y • n = 983	• 7–day food record • dietary intake compared between quintiles according to % energy from added sugars	• strongly significant <u>decline</u> in **nutrient density** for all nutrients (except vitamin C) from low to high quintiles of ***added sugars***
Ballew C, et al., 2000[137]	• CSFII (1994 – 96) U.S. youth • 2 – 17 y • n = 4,070	• 24–hour recall • nutrient intake compared with DRIs	***carbonated soda*** • <u>negatively</u> associated with achieving recommended intake level of **vitamin A**, **calcium** and **magnesium**
Forshee RA, et al., 2001[138]	• CSFII (1994 – 96) U.S. youth 6 – 19 y	• two 24–hour recall	Higher consumption of ***added sugars*** • associated with <u>higher</u> intake of **grains**, **vitamin C**, **iron**, **folates** as well as <u>less</u> **dairy** and **fruits**

Table 2.1 Evidence of associations between added sugar consumption, nutrient/food intake and weight status in children and adolescents (cont'd)

Reference	Participants	Methods	Findings
Johnson RK, et al., 2002[139]	• CSFII (1994 – 96, 1998) U.S. children • 5 – 17 y • n = 3,888	• two 24–hour recall • FM drinkers (3 categories) (i)Nonconsumers (ii) > 0 and ≤ 240 g (iii) > 240 g	***FM*** intake • positively associated with total **milk** intake, energy–adjusted **calcium** and **phosphorous** • negatively associated with **SSB** • **NO** association with %energy from **fat** and **added sugars**
Alexy U, et al, 2003[132]	• German youth • 2 – 18 y • n = 849	• 3–day weighted dietary records	***Added sugar*** intake • positively associated with intake of **total energy**, **sugary foods and beverages** • negatively associated with most **micronutrients** and **nutrient–bearing food groups**
Rodríguez–Artalejo, et al., 2003[140]	• Spanish children • 6 – 7 y • n = 1,112	• FFQ, HEI • comparison between the fifth and the first quintile of SSB consumption adjusted for energy	***SSB*** consumption • associated with lower **milk**, **calcium** and worse **HEI**
Frary CD, et al., 2004[111]	• CSFII U.S. youth • 6 – 17 y • n = 3,038	• two 24–hour recall • 5 categories as major sources of added sugars: SSB, sugars and sweets, sweetened grains, sweetened dairy and pre–sweetened cereal • Compare diet quality by consumption level of the above 5 categories	• ***sweetened dairy*** products and ***pre–sweetened cereals*** has a positive impact on diet quality (**calcium**, **folate**, **iron** and **dairy** servings) • ***SSB, sugars*** and ***sweets***, and ***sweetened grains*** has a negative impact on **diet quality**

Table 2.1 Evidence of associations between added sugar consumption, nutrient/food intake and weight status in children and adolescents (cont'd)

Reference	Participants	Methods	Findings
Joyce T, et al., 2008[133]	• Irish youth 5 – 12 y, n = 594; 13 – 17 y, n = 441	• 7–day food records	high consumption of ***added sugars*** • associated with a decrease in **micronutrient** density of the diet and increased prevalence of **dietary inadequacies**
Libuda L, et al., 2009[143]	• German youth • 2 – 19 y • n = 1,069	• 3–day weighted records	***SSB*** consumption • negatively associated with %energy from **protein**, folate, **calcium** and absolute **diet quality (NQI)**
Wang, et al., 2009[144]	• NHANES (2003 – 2004) U.S youth • 2 – 19 y • n = 3,098	• two 24–hour recall	• Each additional serving (8 oz) of ***SSB*** corresponds to a net increase of 106 **kcal**/d • Replacing all SSB with water could result in an average reduction of 235 kcal/d
Fiorito LM, et al., 2010[145]	• non–Hispanic white girls in U.S. • 5 y at baseline • n = 170	followed–up biennially from age 5 to 15 y • three 24–hour recalls (at age 5, 7 and 9 y, mothers were the primary reporters)	***SSB*** consumers at age 5 y • higher subsequent intake of **soda** and **added sugars**, as well as had lower intake of **milk**, **protein**, **fiber**, **vitamin D**, **calcium**, **magnesium**, **phosphorous** and **potassium** from 5 to 15 y

Table 2.1 Evidence of associations between added sugar consumption, nutrient/food intake and weight status in children and adolescents (cont'd)

Reference	Participants	Methods	Findings
Collison KS et al., 2010[146]	• Saudi Arabia youth • 10 – 19 y • boys (n = 5,033) • girls (n = 4,400)	• 7–day FFQ	***SSB*** consumption • positively associated with **poor dietary choices** (more fast food, savory snacks, iced dessert; less fruits and vegetables, eggs, fish and cereals) • positively associated with **BMI** and **waist circumference** in boys
Fayet, et al., 2013[147]	• Australian National Children's Nutrition and Physical Activity Survey (2007) • 2 – 16 y • n = 4,487	• 24–hour recalls • drinking categories (i) exclusively plain milk drinkers (ii) flavoured milk drinkers (iii) non–drinkers of milk	• ***FM*** drinkers had higher intake of **total milk**, **total sugar**, **energy** and milk–related nutrients (**calcium**, **phosphorus**, **magnesium**, **potassium** and **iodine**) • **NO** between–group differences were observed in **BMI** and **waist circumference**

dietary intakes. Harnack et al. analyzed the two 24–hour recalls of 1,810 U.S. youth (2–18 y) from CSFII 1994 and found that energy intake was positively associated with SSB (defined as non–diet soft drinks) consumption and those in the highest SSB consumption category consumed less milk (calcium, riboflavin, vitamin A and phosphorus) and fruit juice (folate and vitamin C) compared with those in the lowest consumption category (non–consumers)[135]. In another analysis using data from CSFII (1994 – 1996) among 4,070 U.S. youth (2 – 17 y), the authors found that SSB (defined as carbonated soda) consumption was negatively associated with achieving recommended intake level of vitamin A, calcium and magnesium[137]. One study of 1,112 Spanish children (6 – 7 y) compared the dietary intakes between the first and fifth energy–adjusted intake quintile of SSB and found that higher SSB intake was associated with a lower consumption of milk (-88 mL, $P < 0.001$), calcium (-175 mg/d, $P < 0.001$) and a worse HEI (-2 score, $P < 0.01$)[140]. In this study, misreporting may be a limitation considering the food frequency questionnaire (FFQ) was reported by mothers only. The authors also suggested that some potential confounders (e.g., socio–economic status) were warranted for further adjustment when examining the influence of SSB intake on dietary intakes. Libuda et al., examined the 3–day weighted food records from 1,069 German youth (2 – 19 y) and found that SSB consumption was negatively associated with % energy from protein, folate, calcium and absolute diet quality[143]. Wang et al. examined the net caloric impact from replacing SSB with alternatives in 3,098 U.S. youth (2 – 19 y) and found that each additional serving (236 mL) of SSB corresponds to a net increase of 106 kcal/d, while replacing all SSB with water could result in an average reduction of 235 kcal/d[144]. It is important to note that the enlisting of all foods and quantifying portion sizes in these two 24–hour recall may bring potential inaccuracy and bias. In another study, Collison et al. examined 7–day FFQ from 9,433 Saudi Arabia youth and found that SSB consumption was positively associated with poor dietary choices (more fast food, savoury snacks, iced dessert; less fruits and vegetables, eggs, fish and cereals)[146].

To date, there is only one longitudinal study[145] examining the long–term associations between SSB consumption in childhood and dietary intakes over time. Fiorito et al. examined three 24–hour recalls from 170 non–Hispanic white U.S. girls at age 5, 7 and 9 y, with mothers as the primary reporters. After biennial follow–up from 5 to 15 y, the authors found that SSB consumers at age 5 y had higher subsequent intake of soda and added sugars, as well as had lower intake of milk, protein, fibre, vitamin D, calcium, magnesium, phosphorous and potassium. Due to the study design, the external validity of this study may be limited to non–Hispanic white girls only. In addition, studies of dietary patterns find that SSB tend to be consumed in combination with energy–dense foods, such as fast foods, savoury snacks and sweets[149, 150], therefore, higher SSB consumption may be a marker of an overall unhealthy dietary pattern.

2.4.1.3 Flavoured milk

The study by Johnson et al. was the first one to evaluate the nutritional consequences of FM consumption in a representative sample of 3,888 U.S. youth (5–17 y). The authors analyzed the data from CSFII (1994 –96 and 1998) and found that FM intake was positively associated with intake of total milk and energy–adjusted calcium and phosphorous, while was negatively associated with SSB[139]. In addition, no association with added sugars was noticed with FM intake, which may be due to a significantly lower intake of SSB compared between FM and non–FM consumers. Murphy et al. conducted another study on the relationship between FM intakes and diet quality among a large representative sample of 7,557 U.S. youth (2–18 y) from NHANES (1999–2002)[142]. The authors found that drinking FM was positively associated with higher total milk and micronutrients. It is important to recognize that the category of FM drinkers in this study includes youth who may have consumed plain milk as well as FM; therefore total nutrient intakes actually reflect contributions from both types of milk. In a recent study of 4,487 Australian youth (2–16 y), Fayet et al. found that FM drinkers had higher energy–adjusted intake of total milk, total sugar, energy

and milk–related nutrients (calcium, phosphorus, magnesium, potassium and iodine)[147].

Almost all previous studies support the concept of "empty calories" that added sugar intake provides extra energy intake and suggest restricting the intake of added sugars in youths' diet. Although numerous studies have investigated the contribution of added sugar intake on diet quality in youth, the findings vary greatly between studies. Several factors may explain these variations. Firstly, a wide variety of dietary data collection methods are used, including, weighted food record[132, 143], 24–hour recalls (from one day to three day)[135, 137,111, 138, 139, 141, 142, 144, 145, 147], FFQ[140, 146], 3–day records[134], 4–day records[131] and 7–day records[133, 136]. In addition, food and nutrient intakes have been analysed in absolute intakes (grams/day) [111, 131, 139–142, 145, 147] nutrient densities (per 1000 kcal) [133, 135, 136, 141], comparison with DRIs[137] and/or regression coefficients [132, 138, 143] across categories of total sugars[151–153], SSB (ml/d[135, 144–146] or percentage of total energy[143]), FM (grams/d)[139, 142, 147] or intakes of added sugars expressed as (grams/day) [142 111, 134, 138, 140], (grams of added sugar/kcal)[134] and (percentage of total energy) [133 131, 132, 136, 141]. Therefore, standardized methods to determine the impact of added sugars on dietary intakes need to be developed to allow for comparisons between studies and to determine the influence on diet quality in populations[133]. Furthermore, in a recent review, Rennie & Livingstone[154] highlighted that there are wide variations in the definitions of added sugars and diet quality index (Healthy Eating Index[140], Nutritional Quality Index[143], et al.), which represents a further difficulty when assessing associations between intakes of added sugar and diet quality.

Limitations of dietary assessment tools were unavoidable in these studies, such as reporting errors (inaccuracy and bias) by parents or proxy, misreporting of foods and beverages high in added sugars, lacking of long–term usual intake habit[155], potential misclassification as SSB consumers and etc. Non–differential misclassification of persons according to food and nutrients of interest is also

possible. Risk estimates (such as odds ratio or regression coefficient) are likely to be attenuated as a result of the measurement error introduced by few days of dietary recalls. The associations demonstrated in the above studies may be even stronger if the dietary intake, particularly foods and beverages high in added sugars, were accurately reported. Moreover, some studies may be limited by the relatively small sample size (Table 2.2) and external validity. Therefore, it is crucial to have a better understanding of valid approaches to stimulate further progress in this area, including detecting and adjusting misreported nutrient information, energy adjustment, and the evaluation of micronutrient adequacy[156].

2.4.2 Added sugars and metabolic syndrome components

Bray et al. drew attention to the association of obesity with increasing fructose consumption in a landmark paper in 2004[55]. In a review literature by Malik et al. in 2006[92], of the 13 studies conducted among children and adolescents, the majority found significant positive associations or trends towards weight gain. Later, Malik et al., did a meta–analysis evaluating the SSB consumption and BMI in children and adolescents and found a significant positive association between consumption of SSB in every additional serving per day and higher weight gain[157]. Besides the link with elevated risks of adiposity, there is mounting evidence to support the relationship between added sugar intake, primarily in the form of SSB, and higher risk of MetS components[119, 158–160] (i.e., impaired glucose homeostasis and insulin sensitivity, elevated blood pressure, decreased HDL–C, et al.). Controversy between studies may arise from different definition or assessment of added sugar consumption, different study designs, different measures of MetS components, different statistical models to estimate the effect sizes and etc[161].

2.4.2.1 Cross–sectional studies

A large number of cross–sectional studies have been conducted to evaluate the risk association between added sugar intake and MetS components. Since cross–sectional studies usually evaluate the exposure and outcome at the same time

point, they are not able to establish a temporal sequence and infer causality. They are also prone to intractable confounding, reverse causation, and recall bias. For these reasons cross–sectional studies have limited utility in chronic disease epidemiology outside of hypothesis generation[112].

Bremer et al. examined the relationship between SSB consumption and MetS components in 6,967 U.S. youth (12 – 19 y) from NHANES (1999 – 2004) and found that an additional serving of SSB was independently associated with a 5% increase in HOMA–IR, a 0.16–mm Hg increase in systolic blood pressure (SBP), a 0.47–cm increase in waist circumference, a 0.90–percentile increase in BMI and a 0.48–mg/dL decrease in HDL–C concentrations[165] (Table 2.2). Kondaki et al. analyzed data from 546 European adolescents (12.5–17.5 y) and found that frequent consumption of SSB (≥ 5–6 times/week) was related to increased HOMA–IR by 0.281 units[158]. It is important to note that SSB in this study included only coke or other soft drinks; and only frequency was recorded in its FFQ (without quantity information). Welsh et al. examined 2,157 U.S. adolescents (12–18 y) from NHANES (1999–2004) and found that comparing between lowest and highest consumers of added sugars (< 10% vs. ≥ 30% of total energy), added sugar intake was inversely correlated with mean HDL–C (1.40 vs. 1.28 mmol/L, $P = 0.001$), and positively associated with triglycerides (0.81 vs. 0.89 mmol/L, $P = 0.05$). Particularly, among overweight/obese (≥ 85th BMI percentile) adolescents, added sugar consumption was positively associated with HOMA–IR (4.61 vs. 3.49, $P = 0.004$)[159]. One analysis of 1,294 British youth (7–18 y) indicated that the top quantile of SSB (defined as soft drink) consumption was associated with being overweight (odds ratio = 1.67, $P = 0.03$)[163], while another analysis of 9,433 U.S. youth (10–19 y) found that waist circumference and BMI were positively associated with a one–serving higher intake of SSB in boys only[146].

Evidence has been emerging but yet inconclusive to suggest that increased consumption of added sugars might raise blood pressure (BP)[75], which were

Table 2.2 Evidence of associations between added sugar consumption and MetS components in children and adolescents from cross–sectional studies

Reference	Participants	Methods	Findings
Davis JN, et al., 2005[162]	• Latino children • 9 – 13 y • overweight • n = 63	• 3–day records • covariates: age, sex, fat mass, Tanner stage and energy intake.	• ***SSB***: negative association with lower **acute insulin response** and **β cell function** (disposition index)
Davis JN, et al., 2007[47]	• Latino youth • 10 – 17 y • overweight • with a family history of T2DM • n = 120	• two 24–hour recalls • covariates: sex, Tanner stage, energy intake, fat–free mass, and noncarbohydrate macronutrient intake.	**total sugar** • positively correlated with **BMI**, **BMI z–score** and **total fat mass** • negatively correlated with **insulin sensitivity** and **β cell function**
Gibson S, et al., 2007[163]	• British youth • 7 – 18 y • n = 1, 294	• 7–day weighted food records	• % energy from **NMES** (non–milk extrinsic sugars) or soft drinks was weakly inversely associated with **BMI z–score** • top quantile of ***soft drink*** consumption was associated with **overweight**
Nguyen et al., 2009[164]	• NHANES (1999 – 2004) • U.S. adolescents (12 – 18 y) • n = 4,867	• single 24–hour recall • SSB categorized by number of ounces consumed per day	***SSB*** (lowest vs. highest vs. category) • a 0.2 mg/dL higher in **serum uric acid** • a 0.2 SD higher in **systolic BP z–score**

Table 2.2 Evidence of associations between added sugar consumption and MetS components in children and adolescents from cross–sectional studies (cont'd)

Reference	Participants	Methods	Findings
Bremer et al., 2009[165]	• U.S. adolescents • 12 – 19 y • n = 6,967	• NHANES (1999 – 2004) • 24–hour recall • covariates: age, sex, race and energy intake	Higher ***SSB*** consumption (compared with lowest quintile, 2nd to 4th quintile and highest quintile) • Higher **HOMA–IR**, **systolic BP**, **waist circumference**, **BMI percentile** • Lower **HDL–C**
Casazza K et al., 2009[166]	• U.S. children • 7 – 12 y African–American (n = 79) White (n = 68) Hispanic (n = 55)	• two 24–hour recalls	Greater energy from ***CHO*** • positively associated with greater **waist circumference**, higher **triglyceride** and **fasting glucose**
Sharma S, et al, 2010[167]	• African American children • 9 – 11 y • Overweight (BMI > 85th percentile), without metabolic disease • n = 95	• Three–day food diaries • Added sugars – MyPyramid Equivalents Database (1994 version) • Covariates: sex, pubertal stage and waist circumference	• Higher ***added sugar*** intake is associated with higher **triglyceride** and **HOMA–IR** • similar results were found for ***SSB***.

Table 2.2 Evidence of associations between added sugar consumption and MetS components in children and adolescents from cross–sectional studies (cont'd)

Reference	Participants	Methods	Findings
O'Neil CE, et al., 2011[168]	• U.S. youth • 2 – 13 y • n = 7,049	• NHANES (1999 – 2004) • single 24–hour recall • Added sugars – Food and Nutrient Database for Dietary Studies & USDA Survey Nutrient Database • Compared between candy consumers vs. non–consumers	• **Candy** consumers had higher intake of **energy** and **added sugars**; • **No** difference in **HEI** score • **weight**, **BMI**, **BMI z–score** and **waist circumference** were lower in candy consumers • **No** difference in **blood pressure**, blood **lipids**
Welsh JA, et al., 2011[159]	• U.S. adolescents • 12 – 18 y • n = 2,157	• NHANES (1999 – 2004) • Single 24–hour recall • Added sugar levels: < 10%, 10 – 15%, 15 – 20%, 20 – 25%, 25 – 30% and ≥ 30% of total energy • covariates include BMI, socioeconomic status, energy intake and physical activity	***Added sugar*** consumption • positively associated with lower **HDL–C**; higher low-density lipoprotein (**LDL–C)**, **triglyceride** and **HOMA–IR**
Valente H, et al., 2011[161]	• Portugal school children • 5 – 10 y • n = 1,675	• semi–quantitative FFQ by parents • SSB (3 categories): < 1 serving/d (referent) 1 – 3 servings/d > 3 servings/d • body weight cut–off: Overweight: > 25 kg/m^2	• ***SSB*** intake was **NOT** associated with increased risk of **overweight**

Table 2.2 Evidence of associations between added sugar consumption and MetS components in children and adolescents from cross–sectional studies (cont'd)

Reference	Participants	Methods	Findings
Nicklas TA, et al., 2011[169]	• NHANES (2003 – 2006), U.S. youth • 6 – 18 y • n = 3,136	• single 24–hour recalls • covariates: age, sex, race, poverty income ratio, energy intake and physical activity	• **NO** associations were observed between added sugar intake and **adiposity** measures (**BMI**, **BMI z–score** and **waist circumference**)
Kondaki K, et al., 2013[158]	• European Adolescents at schools • 12.5 – 17.5 y • n = 546	• FFQ (only frequency) • Covariates: sex, Tanner stage, energy intake, physical activity and BMI percentile	• **HOMA–IR** is higher among adolescents consuming ***SSB*** (5 – 6 times/week) compared with consuming ≤ 1 times/week by 0.281 units

primarily from adults, with only one study from youth. Among 4,867 U.S. adolescents (12–18 y) from the NHANES (1999–2004), Nguyen et al. found that higher SSB consumption was associated with higher serum uric acid (+0.18 mg/dL, $P = 0.01$) levels and SBP (+0.17 z-score, $P = 0.03$)[164]. Because the dietary recall did not specifically include intake of other sweets, particularly candies, baked goods, and other sweet snacks that may be consumed across the groups, the observations could be an underestimate of the impact of total sugar and HFCS intake. In addition, the lack of information of family history of gout and hypertension may affect the relationship. A recent report of data from 4,528 U.S. adults without previous history of hypertension who participated in the NHANES (2003–2006) showed that an increased fructose intake ≥ 74 g/d (corresponding to 2.5 serving of SSB) was independently and significantly associated with higher odds of elevated BP levels – 26%, 30% and 77% higher risk for BP cut–offs of ≥135/85, ≥140/90, and ≥ 160/100 mm Hg, respectively[170], after adjusting for age, sex, race, smoking, diabetes, physical activity, BMI, total energy intake, and dietary confounders such as total carbohydrate, alcohol, salt and vitamin C intake. In contrast, among longitudinal studies based on U.S. nurses and health professionals, Forman et al. did not find an association between fructose consumption and hypertension[171]. However, it was noticed that among those participants, a large amount of fructose was consumed from natural fruits, of which the high content of antioxidants and flavenols have been shown the ability to block the pro–hypertensive effects of fructose in animals. In addition, ascorbate from natural fruits also lowers uric acid by stimulating renal excretion.

Besides the evidence from above large sample–size investigations, there were also several small studies examining the relationship between added sugar consumption and risk of MetS components. Davis et al. performed the cross–sectional analysis among 63 Latino overweight children (9–13 y) and found a negative association between SSB intake and acute insulin response ($\beta = -0.219$, $P = 0.072$) and β cell function ($\beta = -0.298$, $P = 0.077$)[162]. In another analysis of 120 overweight Latino youth (10 – 17 y), dietary sugar intake was found to be

associated with higher BMI and total fat mass (r = 0.20, r = 0.21, respectively, P = 0.05) as well as lower insulin sensitivity (r = -0.29, $P < 0.05$)[47]. This study may be limited by its self–reported dietary recalls only on weekdays. In addition, different from other studies, the definition of sugar in this study includes both added and naturally occurring sugars. Casazza et al. examined a sample of U.S. children (7–12 y) from diverse groups (African–American, n = 79; White, n = 68; Hispanic, n = 55) and reported that greater energy from carbohydrates was positively associated with greater waist circumference, higher triglycerides and fasting glucose[166]. However, this study did not specifically examine energy intake from added sugars. Sharma et al. assessed among 95 African American children who were overweight (9–11 y) and found that higher added sugar consumption was linked to higher triglycerides and HOMA–IR[167]. The generalizability of this study may probably be restricted to overweight African American children from low–income families.

In addition, negative findings also exist. In a recent study of 1,675 Portuguese schoolchildren (5 – 10 y), the authors found the intake of SSB was not associated with increased risk of overweight[161]. It is important to note that the definition of SSB in this study included fruit juices, which are usually excluded in subcategories of SSB. Nicklas et al. examined 3,316 U.S. youth (6–18 y) from NHANES (2003–2006) and found no significant associations between added sugar intake and adiposity measures (BMI, BMI z–score, waist circumference, triceps and subscapular skinfolds)[169]. Besides adjusting for age, sex, total energy intake and physical activity, this study also controlled for race and poverty income ratio, considering the socio–demographic differences in the added sugar consumption among adults[172]. In addition, overweight and obese youth in this study reported a lower mean energy intake than the normal–weight children, which could reflect the underreporting of food intake is more pervasive among youth with higher BMI. After deleting potential misreporting, still no associations were found between added sugar intake and any of the adiposity measures. The association between added sugar intake and adiposity (BMI) is not conclusive in a

study of 4–year (n = 391), 9–year (n = 810) and 13–year (n = 1,005) Norwegian youth that positive and negative associations were observed among 4–y boys and 13–y girls, respectively[131]. But it is important to note that height and weight were all self–reported and obtained from only 70 – 80 % of the participants, which may disturb the true relationship. In addition, these negative findings are possibly due to very low SSB consumption [173] or the under–reporting in parental recall of their children's food intakes[161].

To date, all studies on FM among youth were focused on the relationship with adiposity, but not with other MetS components. An examination of 7,557 U.S. youth (2–18 y) from NHANES (1999–2002) found that drinking FM is not associated with adverse effects on BMI measures[142]. Another cross–sectional study analyzed 4,487 children (9–16 y) from 2007 Australian National Children's Nutrition and Physical Activity Survey and also found that no differences were observed in BMI and waist circumference between FM and non–FM consumers[147].

2.4.2.2 Longitudinal studies

The longitudinal design has the nature strength in studying changes over time in added sugar intakes and in MetS components measures while accounting for growth and maturation[112]. However, different than intervention trial studies, residual and unmeasured confounding is still possible despite extensive adjustment for many important covariates[174].

Ludwig et al. examined 548 U.S. schoolchildren (11.7 ± 0.8 y) and found that each additional serving of SSB consumption at baseline was independently associated with an increase in BMI (+0.24 kg/m^2, 95% CI 0.10 – 0.39; $P = 0.03$) and higher risk of being obesity (odds ratio = 1.60, 95% CI 1.14 – 2.24; $P = 0.02$) after 19 months[175] (Table 2.3). This study provided the first longitudinal evidence linking SSB consumption and weight gain in children. Although BMI is in widespread use, and provides a good estimate of adiposity in children[176], it alone

cannot fully control for changes in body composition over time, resulting from puberty or activity changes. In addition, random error in the measurement of SSB consumption and inaccuracy in the estimation of adiposity by BMI, could lead to underestimation of actual effects[175]. Findings from the U.S. Growing Up Today study[174] which examined 16,771 children and adolescents (9 – 14 y at baseline) over two 1–year periods showed that increased consumption of SSB was associated with higher BMI gains from the prior year in both boys (+0.03 kg/m^2 per daily serving, $P = 0.02$) and girls (+0.02 kg/m^2, $P = 0.096$). Further adjusting for total energy intake substantially reduced the estimated effects, which were no longer significant, but it may not be appropriate to control for energy intake if the exposure is high sugar which leads to high energy intake. A major limitation of this study was the necessity of data collection (including height and weight) all finished by self–report on mailed questionnaires. For example, no specific number of mL in a can or glass was set for SSB in the FFQ, of which the confusion may lead to random report errors. A retrospective cohort design was used to examine the association between SSB consumption and overweight at 1–year follow–up among 10,904 U.S. preschool children who were aged 2 and 3 years[177]. Among children who were normal or underweight at baseline (BMI < 85^{th} percentile), the association between SSB consumption and development of overweight was not observed. Children who were overweight or obese at baseline (BMI ≥ 85^{th} percentile) and consumed 1 to < 2 drinks/day (2.0, 95% CI 1.3 – 3.2), 2 to < 3 drinks/day (2.0, 95% CI 1.2 – 3.2), and ≥ 3 drinks/day (1.8, 95% CI 1.1 – 2.8) had a higher odds ratio to remain overweight as the referent (< 1 drink/d). Considering the younger age of preschool children, all dietary assessments were done by their parents which may lead to biased reporting.

A 21–year follow–up longitudinal study of 2,139 Finnish youth (aged 3 – 18 y at baseline) found that the increased consumption of SSB from childhood to adulthood was directly associated with BMI and being overweight in adulthood in women (odds ratio = 1.90, 95% CI 1.38 – 2.61). But the changes in sweet consumption were not associated with BMI in adulthood[178]. Since portion sizes of

SSB and sweets were not reported in the FFQ, and the considerable changes in portion sizes over this long–term period, it is possible that the overweight participants actually consumed sweets and soft drinks less often than their normal–weight peers, but ate or drank larger portions, thus consuming comparable or even greater amounts of sweets or soft drinks. Given the timing of the study, they may have been dealing with smaller portion sizes, considering the portion sizes of many foods, such as soft drinks and sweets, have increased in the last few decades around the world[180, 181]. In addition, the sex difference existed in this study may be explained as SSB consumption could be a better marker of unhealthy eating behavior in women than in men[178]. In another longitudinal study, a total of 170 non–Hispanic white girls from U.S. were assessed biennially from age 5 to 15 y[182]. The authors reported that greater SSB consumption (≥ 2 servings/d) was associated with a higher percentage of body fat, waist circumference and weight over time than the referent (<1 serving/d). This study offers advantages over previous longitudinal research by assessing SSB intake and adiposity measures repeatedly over 10 y. In addition, this study examined several different beverages and found only SSB showed significant positive association with adiposity. Another important difference is the definition of SSB in this study included coffee and artificially sweetened beverages.

Referring to FM, there is only one longitudinal analysis of 2,270 British children (10 y at baseline) which indicated similar associations of FM consumption with body weight between FM and non–FM consumers. However among overweight/obese children, those who consumed FM gained more body fat over 2 years compared with non–FM consumers, while no effects were seen among healthy–weight children[179]. In this study, dietary assessment was performed only at baseline, and therefore the association between changes in FM consumption and changes in body composition was not evaluated. In addition, considering the low variability in FM intakes, it was not analyzed as a continuous variable.

Table 2.3 Evidence of associations between added sugar consumption and MetS components in children and adolescents from cohort studies

Reference	Participants	Methods	Findings
Ludwig DS, et al., 2001[114]	• U.S. school children • mean aged 11.7 y at baseline • n = 548	• follow–up for 19 months • FFQ • covariates: baseline age, sex, race, BMI, diet (% energy from fat, energy–adjusted fruit juice), physical activity and total energy intake.	• each additional serving of ***SSB*** is associated with 0.24 kg/m^2 higher **BMI** • baseline ***SSB*** is associated with a mean change in **BMI** (+0.18 kg/m^2) for each serving
Berkey CS, et al. 2004[174]	• U.S. youth • 9 – 14 y at baseline • n = 16,771	• FFQ • follow–up over two 1–year period • covariates: race, height, menstrual status, Tanner stage, prior BMI z–score, physical activity and energy intake	• ***SSB*** consumption was associated with a small extra **weight gain** (boys: +0.03 kg/m^2, girls: +0.02 kg/m^2, per daily serving)
Welsh JA, et al., 2005[177]	• n = 10,904 • children • 2 – 3 y at baseline	• Retrospective • FFQ at baseline • covariates: age, sex, race, birth weight, intake of high–fat foods, sweet foods and total energy.	Referent (< 1 drink/d ***SSB***) • 1 to < 2 drinks/d: 2.0 times • 2 to 3 drinks/d: 2.0 times • ≥ 3 drinks/d: 1.8 times to become **overweight**

Table 2.3 Evidence of associations between added sugar consumption and MetS components in children and adolescents from cohort studies (cont'd)

Reference	Participants	Methods	Findings
Johnson L, et al., 2007[173]	• British children • 5 y, n = 521 7 y, n = 682	• follow–up at age 9 y • fat mass (DXA) • 3–d food diaries	• **NO** association between ***SSB*** consumption at 5 or 7 y of age and **total fat mass** at age 9 y.
Nissinen K, et al., 2009[178]	• Finnish youth • 3 – 18 y at baseline • n = 2,139	• 21–year follow–up • FFQ • liquid: SSB • solid: sweets	• In women, the increase in ***SSB*** consumption from childhood to adulthood is associated with **BMI** in adulthood (+0.45 kg/m^2), and with being **overweight** (OR = 1.9) • **No** association between overweight in adulthood and sweet consumption in childhood or the change in consumption from childhood to adulthood
Fiorito LM, et al., 2009[145]	• non–Hispanic white girls in U.S. • 5 y at baseline • n = 170	• followed–up biennially from age 5 to 15 y • three 24–hour recalls (at age 5, 7 and 9 y, mothers were the primary reporters) • categorized as consuming < 1, ≥ 1 and 2, or ≥ 2 serving of SSB at baseline	• greater ***SSB*** consumption at 5 y (≥ 2 serving/d) associated with a higher % **body fat**, **waist circumference** over 10 years
Noel SE, et al., 2012[179]	• British children • 10 y at baseline • n = 2,270	• 3–day food diary • DXA measurement at 11 and 13 y • FM consumer vs. non–consumer • physical activity (accelerometer)	• Overweight/obese children who consumed ***FM*** had less favourable 2–year changes in **body fat** compared with non–consumers (–0.2% vs. –3.4%)

To date, only one cohort study reported negative findings. Johnson et al., examined among 1,203 British children and found no evidence of an association between SSB consumption at age 5 or 7 y and total body fat mass at 9 y173. The authors proposed two possible explanations: (i) children display better compensation for liquid energy than adults183, 184; (ii) SSB consumption may be too low (57–67 g/d on average) in this study to have an impact on fatness, which is much lower than the reported amounts in the U.S. studies.

2.4.2.3 Intervention trials

Previous intervention trial studies may have yielded inconsistent results because of small samples, short duration, poor adherence, or lack of individual randomization[110, 120, 121, 185]. Short term experimental studies are not well suited to capture long–term patterns since compliance tends to wane with increasing duration but they do provide important insight into potential underlying biological mechanisms[96].

James et al. performed a cluster randomized controlled trial (RCT) in 644 children (7–11 y) from 6 primary schools in southwest England by providing focused educational program on nutrition over one school year[120] (Table 2.4). It was found that SSB consumption decreased by 150 mL on average and the percentage of overweight and obesity decrease by 0.2% in the intervention group, while SSB consumption increased by 50 mL on average, and the percentage of overweight and obesity increased by 7.5% in the control group. The low return rate of food diaries may bring in response bias and the randomization in this study was based on classes (not schools), thus transfer of knowledge may have taken place outside the classroom. In a study to examine the effect of decreasing SSB consumption on body weight, 103 U.S. adolescents (13–18 y) who regularly consumed SSB were randomly assigned to intervention and control groups[121]. The intervention was designed as home-delivery of noncaloric beverages to displace SSB. After 25 weeks, it was noticed that the changes in BMI between the intervention and control groups were not significant overall. However, in the intervention group,

Table 2.4 Evidence of associations between added sugar consumption and MetS components in children and adolescents from experimental trial studies

Reference	Participants	Methods	Findings
James J, et al., 2004[120]	• Children from 6 primary schools in southwest England • 7 – 11 y • n = 644	• Cluster RCT • Intervention: focused educational program on nutrition over one school year • 3–day food diary (2 weekdays + 1 weekend day)	Intervention group: • ***SSB*** consumption decreased by 0.6 glasses on average • Percentage of **overweight** and **obesity** decrease by 0.2% Control group: • SSB consumption increased by 0.2 glasses on average • Percentage of overweight and obesity increase by 7.5%
Ebbeling CB, et al., 2006[121]	• Adolescents who regularly consumed SSB • 13 – 18 y • n = 103	• 25 weeks • Intervention: home deliveries of non–caloric beverages to replace SSB	• Consumption of ***SSB*** decreased by 82% in the intervention group and no change in control group • Subjects in the upper baseline–BMI tertile, **BMI** change differed significantly between intervention (–0.63 ± 0.23 kg/m^2) and control (+0.12 ± 0.26 kg/m^2) group
Davis JN, et al., 2007[186]	• Latina female adolescents • 12 – 17 y • overweight (≥ 85th BMI) • n = 16	• 12–week pilot intervention class (reduction to a goal of 10% or less of total energy intake from added sugars, through SSB, candy and sweets) • 3–day diet records • DXA, OGTT	• <u>reduction</u> in ***added sugar*** intake leads to improvement in **insulin secretion**

Table 2.4 Evidence of associations between added sugar consumption and MetS components in children and adolescents from experimental trial studies **(cont'd)**

Reference	Participants	Methods	Findings
Ventura E, et al., 2009[187]	• Latino adolescents • mean aged 15.5 y • n = 54	• secondary analysis of a RCT • 16–week intervention class to decrease added sugar intake • nutrition–only group: 1 nutrition class per week • nutrition plus strength training • control group: no intervention	• reduction in ***added sugar*** intake by the equivalent of 1 can of soda per day lead to an improvement in **glucose** increment area under the curve and **insulin incremental** area under the curve
Ebbeling CB, et al., 2012[115]	• overweight/obese adolescents who regularly consumed SSB • mean aged 15 y • n = 224	• experimental group: 1–year intervention to decrease SSB consumption, with 1 year follow–up without intervention • home–delievery of noncaloric beverages every 2 weeks; monthly telephone calls; 3 check–in visits	• similar reported ***SSB*** consumption at baseline between groups (1.7 serving/d) and declined to nearly 0 in experimental group • the change in mean **BMI** at 2 years did **NOT** differ significantly between two groups • significant between–group differences for changes in **BMI** (–0.57 kg/m^2) and **weight** (–1.9 kg) • modification effect on ethnic group (significant in Hispanic, but not non–Hispanic)
de Ruyter JC, et al., 2012[116]	• normal–weight Dutch children • 4 – 11 y • n = 641	• 18 month double–blinded RCT (beverages to schools) • sugar–free group: 250 mL artificially sweetened beverage per day • sugar group: 250 mL SSB (104 kcal) per day	• **BMI z–score** increased on average by 0.02 SD in sugar–free group and by 0.15 SD in ***sugar group*** • **weight** increased by 6.4 kg in sugar–free group and by 7.4 kg in sugar group • **waist–to–height ratio**, **fat mass** also increased significantly more in ***sugar group***

those adolescents in the upper BMI tertile at baseline showed a decrease in their average BMI (–0.64 ± 0/23 kg/m^2) compared with the counterparts in the control group, who had an increase in their average BMI (+0.12 ± 0.26 kg/m^2), and the net effect of (0.75 ± 0.34) kg/m^2 was statistically significant. The strengths of this study include a novel environmental intervention, a demographically diverse sample and a 100% completion rate. However, considering this is a pilot study, it is limited by the relatively small sample size and short intervention period.

Ventura et al. performed a secondary analysis of a RCT in 54 Latino overweight adolescents (mean age 15.5 y)[187]. During the 16–week intervention, the experimental group was given a nutrition class per week, while no such nutrition class for the control group. After the intervention, it was found that adolescents in the intervention group decreased added sugar intake by an average of 47 g per day (equivalent to the sugar content in 355 mL of soda) and had an improvement in glucose increment area under the curve and insulin incremental area under the curve assessed during an OGTT, while the changes in BMI and total fat mass were not statistically significant. In another intervention pilot trial, 16 overweight Latina adolescent females (12 – 17 y) were given a nutrition class intervention to reduce added sugar towards a goal of 10% or less of total energy intake through a reduction in SSB, candy, syrups and sweets. After the 12–week intervention, it was found that participants with greater reductions in added sugar intake showed significantly greater improvement in insulin secretion, independent of age, sex, BMI z–score and baseline insulin secretion ($r = 0.85$, $P < 0.05$)[186]. Considering this is a pilot study, it is naturally limited by its fairly small sample size, short intervention period. The lack of a control group is another limitation; the initial design was to assess the difference between an individualized, home–based format versus a group, classroom–based format using an identical nutrition curriculum, but the authors combined those two groups due to the similar changes in outcomes.

There were two recent studies published in *N Engl J Med* examining the effect of decreasing SSB consumption on weight status among youth population. Ebbeling[115] and colleagues randomly assigned 224 overweight and obese adolescents who regularly consumed SSB to experimental and control groups. The experimental group was designed to receive a 1–year intervention with home delivery of noncaloric beverages to decrease consumption of SSB. After a follow–up for an additional year, it was observed with non-significant changes in BMI at 2 years between the experimental and control groups. However, at 1 year, there were significant changes in BMI (β = -0.57 kg/m^2, P = 0.045) and weight (β = -1.9 kg, P = 0.04) particularly among Hispanic participants. These modest changes (not sustained at 2 years) were mainly occurring in the small subset of obese Hispanic adolescents. A particular advantage of this study is its intervention was placed at home, considering the greatest SSB intake among youth occurs at home[114]. The other study by de Ruyter and colleagues clearly suggested that masked replacement of 250 mL SSB (104 kcal) with a sugar–free beverage significantly reduced weight gain (+0.02 vs. +0.15 SD of BMI z-score, 95% CI of the difference -0.21 to -0.05) and fat accumulation (+6.35 kg vs. +7.37 kg, 95% CI of the difference -1.54 to -0.48) in normal–weight children (4–11 y). The observed significant differences in body fat and BMI z–score can be ascribed primarily to the assigned beverage, considering the mean changes in other factors that affect weight were assumed to be similar between groups. This study is laudable for its double–blind design (eliminate the effects of psychological cues and socially desirable behavior), large sample of normal–weight schoolchildren (n = 641) and long duration of 18–month (ensure that observed effect was not transient)[116]. The stratified randomization also produced well–balanced study groups at baseline. This study does not support the findings from some observational studies from both youth and adults that the consumption of artificially sweetened beverages is associated with weight gain[188, 189]. The authors noted that individuals who are at risk of gaining weight may turn to artificial sweeteners in an attempt to reduce caloric intake[188, 189]. It is possible that consumers may also believe that the intake of such artificial sweeteners permits

them to eat more of other foods, which may lead to a net increase in total caloric intake[189]. The epidemiologic association of the use of artificial sweeteners with obesity does not show that switching to artificially sweetened beverages by itself alone is sufficient to combat weight gain[116].

To date, all trial studies examining sugar intake and blood pressure were conducted among adults. For example, an intervention trial[190] by administration of supplemental fructose (200 g/d) for 2 weeks induced significant increases in both systolic (7 ± 2 mm Hg, $P < 0.004$) and diastolic BP (5 ± 2 mm Hg, $P < 0.007$) in healthy adult men in association with a significant rise in fasting levels of serum uric acid (309 ± 12 μmol/L, $P < 0.0001$). Fructose ingestion also resulted in a significant increase in BMI (0.2 SD of z-score, $P = 0.003$), fasting serum triglycerides (0.62 ± 0.23 mmol/L, $P < 0.001$), insulin (14.6 ± 3.5 pmol/L, $P < 0.001$) and HOMA–IR (0.57 ± 0.16 unit, $P < 0.005$) as well as a decrease in HDL–C. In an 18–month intervention trial in adults, the reduction in SSB (1 serving/day) was associated with a 1.8 mm Hg (95% CI 1.2 to 2.4) reduction in systolic BP after controlling for BMI[191]. To our knowledge, there are only two studies that suggest that fructose intake does not influence the risk of developing hypertension, but the data are from self–reported hypertension[171, 192].

2.4.3 Different effects between liquid and solid added sugars

As acknowledged in the AHA statement, the form in which added sugars are consumed seems to be an important modifier of the effects of micronutrient dilution[156]. A meta–analysis of studies over 25 years suggests that there is more precise compensation for the energy challenge following solid food consumption compared with semi–solid or, especially liquid foods, following covert manipulation of the energy composition of foods[91].

To date, most studies comparing the different effects between liquid and solid added sugars are from intervention trial studies among adults. In an early cross–over design, 7 male and 8 females (mean aged 22.8 y) were given sugar loads

Table 2.5 Evidence of RCT comparing the effects on energy intake and weight gain between consumption of liquid and solid added sugars in adults

Reference	Participants	Methods	Findings
DiMeglio, et al., 2000[193]	• 7 male + 8 female • mean aged 22.8 y	• crossover • two 4–week period + one 4–week washout • 450 kcal/d CHO load ***Liquid***: soda; ***Solid***: jelly beans	• Daily energy intake higher with load in liquid vs. solid • **body weight** & **BMI** increased only during liquid load
Almiron–Roig, et al., 2004[194]	• 16 male + 16 female • 18 – 35 y	• Crossover 300 kcal preload followed by ad lib lunch ***Liquid***: regular cola; ***Solid***: fat–free cookie	**NO** difference in satiety or in subsequent **energy** intakes
Mourao et al., 2007[195]	• 120 adults Lean (n = 60) Obese (n = 60) • 18 – 50 y	• Cross–over • carbohydrate load **Liquid**: watermelon juice **Solid**: watermelon	• The liquid form elicited a weaker compensatory dietary response than the matched solid form • total daily energy intake was significantly higher by 12.4% on days when liquid form was ingested • overall differences between lean and obese participants were small and not systematic
Chen, et al., 2009[196]	• U.S. adults • 25 – 79 y • n = 810	• RCT (behavioral intervention) • 18 months • 24–hour recalls (1 weekday + 1 weekend day) at baseline, 6 mo and 18 mo ***Liquid***: SSB; ***Solid***: all other calorie	• ↓ liquid calorie (***SSB***) intake had stronger effect on weight loss than ↓ ***solid*** calorie • Reduction in ***SSB*** intake of 1 serving/d was associated with a **weight loss** of 0.5 kg at 6 mo and of 0.7 kg at 18 mo

(450 kcal/d) as a liquid (soda) or solid (jelly beans) in a duration of two 4–week periods separated by a 4–week washout and it was found that only liquid sugars promoted positive energy balance and body weight (BMI) increased significantly only during the liquid period[193] (Table 2.5). This study provided evidence that compensatory dietary responses to added sugars in liquid form are less evident than those to isoenergetic solid loads. Because of the within–subject design, individual reporting biases and inaccuracies in 24–hour recalls would likely have held equally during both treatment groups. But, it is important to note that the forms of carbohydrate were not perfectly matched in this study because soda contained HFCS as the predominant sweetener, whereas the jelly beans were high in sucrose. The higher fructose load in soda is expected to be more satiating, based on the glucostatic theory of hunger[197]. Almiron–Roig et al. performed another cross–over interventional trial in 32 adults (16 men and 16 women, aged 18 – 35 y) by providing equal–energy preloads (300 kcal) of regular cola and fat–free raspberry cookies followed by *ad lib* lunch[194]. The authors reported no differences in satiety or subsequent energy intake between experimental groups. This study provided reverse evidence comparing with the above study that an beverage acted no differently on hunger or satiety than did a solid food, and had no different impact on energy intakes at the next meal. Since it is a short–term interventional trial, whether energy is provided in solid or liquid form may be less important than is the time of preload ingestion relative to the test meal[194]. In another cross–over design, Mourao et al. provided a carbohydrate load in liquid (watermelon juice) and solid (watermelon) form separately to 120 adults (18 – 50 y) and found that the liquid form induced a weaker compensatory dietary response than the matched solid form and thus total daily energy intake was significantly higher by 12.4% on days when liquid form was ingested[195]. As expected, beverages have lower satiety value, lower demand for oral processing and shorter gastrointestinal transit times[195]. In an 18–month prospective randomized controlled behavioral intervention trial of 810 adults (25 – 79 y), Chen et al. found that a reduction in liquid (SSB) energy intake of 100 kcal/d had a stronger effect (-0.49 kg, 95% CI 0.11 – 0.82, $P = 0.006$ at 6 month; -0.65 kg, 95% CI 0.22 –

1.09, $P = 0.003$ at 18 month) than did a reduction in energy from intake of solid foods (on weight loss[196]. Strengths of this study included its longitudinal design and long–term duration, its relatively large sample size, the availability of six 24–h diet recalls (one from a weekday and one from a weekend day at each of the 3 time points over 18 months) to measure dietary intake and the high rates of retention.

To our knowledge, there are only two observational studies in youth to investigate the differences between consumption of added sugars from solid and liquid sources. One came from a cross–sectional analysis of 3,038 U.S. youth (6 – 17 y) from CSFII (1994 – 96, 1998) which reported that sweetened dairy products and pre–sweetened cereals have a positive impact on diet quality (calcium, folate, iron and dairy servings), while SSB, sugars and sweets, and sweetened grains have a negative impact on diet quality (fruits and dairy servings)[111]. These associations may be attributed to many children eating more meals and snacks at restaurants and fast food establishments where they consume less fruits and dairy products in comparison with home[198]. In addition, intake of foods high in saturated fat that may typically be eaten when drinking SSB, whereas pre–sweetened cereals may usually be consumed together with yogurt or milk. The other came from a 21–year follow–up study of 2,139 Finnish youth (3 – 18 y at baseline) which found that consumption of added sugars from either liquid (SSB) or solid (sweets) sources in childhood and adolescence were not associated with BMI in adulthood[178]. This may partly due to the limitation of its dietary assessment method of FFQ, which only recorded frequency but not absolute amounts consumed. But it also noticed that the increase consumption of SSB from childhood to adulthood was associated with being overweight in women (not in men) and no such association was found with consumption of sweets. SSB consumption could be a better marker of unhealthy eating behavior in women than in men[178]. Another analysis of 7,049 children (2 – 13 y) and 4,132 adolescents (14 – 18 y) from NHANES (1999 – 2004) found that compared to non-consumers, adiposity indicators (weight, waist circumference, BMI,

percentiles/z–score for weight–for–age and BMI–for–age) were lower for candy consumers[168]. This study provided further evidence on the relationship between solid added sugars (candy) and adiposity indicators, but it did not compare candy with liquid added sugars.

2.4.4 Potential mechanisms

There are several potential mechanisms that may account for the different effects between consumption of energy from liquid and solid foods. Firstly, the act of masticating the solid may provide an internal satiety signal not triggered by simply swallowing the liquid[193, 199]. Both early pancreatic exocrine and endocrine responses to oral stimulation with viscous or solid stimuli are greater than those to fluids[193, 200]. A cephalic phase release of the purported satiety promoting peptide, cholecystokinin has also been demonstrated with a solid meal, but never contrasted to responses following oral exposure to a fluid[201]. Secondly, there are often large differences in the volume, energy density and osmotic properties of most liquids and solids. Meals of larger volume, lower energy density and lower osmotic potential are emptied from the stomach at a quicker rate. Beverages are emptied at a higher rate from stomach than solids which may induce weaker signals in the gastrointestinal tract and lead to inhibition of further food intake[202]. Thirdly, cognition may also play a role that if solid foods are considered higher in energy content, it could lead to reduced intake[203] Lastly, discrepant metabolic and cardiovascular responses to liquid and solid meals may contribute through an influence on energy expenditure, which is higher acutely after ingestion of a solid meal compared to an isoenergetic, high carbohydrate liquid meal[204]. Considering a weaker satiety signals triggered from caloric beverages, weight gain is assumed to arise with greater energy intake from liquid rather than from solid foods; therefore, total energy intake may be greater with liquid energy intake than with consumption from solid foods[193, 195, 205].

The prevailing mechanisms linking added sugar intake (particularly from SSB) to weight gain are decreased satiety level and reduced compensation in further food

intake at subsequent meals with consumption of liquid energy, leading to an increase in total energy intake[91, 193]. However, the specific mechanism responsible for the weaker compensatory responses to liquid is unknown yet[206]. For the same individual who remains a similar level of physical activity, if dietary intake does not decrease by an equivalent energy amount from SSB, then positive energy balance and gains in weight were expected[93]. This has been testified in short–term feeding trials in adults that showed greater energy intake and weight gain after SSB intake, compared with noncaloric artificially sweetened beverages[185]. In addition, several trial studies in adults have shown that greater energy intake and weight gain after isocaloric consumption of added sugars from liquid as opposed to solid source[91, 193, 205]. These studies suggest that liquid added sugars may not suppress intake of solid foods to maintain energy balance. Another plausible explanation for the observed reduction in body fat is that the removal of sugar from liquid sources was not sensed by satiating feedback system and was not fully compensated for with further consumption of other foods[207]. It is assumed that reduced ingestion of liquid added sugars might also reduce the insulin spike and thus diminish hunger[88]. However, the evidence supporting this hypothesis remains inconclusive[208].

Over the past decade, numerous studies have found that an elevated serum uric acid level predicts the development of hypertension[209]. The mechanism by which serum uric acid mediates hypertension and MetS is still under study. Uric acid has multiple effects on endothelial cells, vascular smooth muscle cells, and adipocytes. Some of the effects include the inhibition of endothelial Nitric Oxide levels, the stimulation of inflammatory pathways including C–reactive protein, the stimulation of local angiotensin II production, the stimulation of nicotinamide adenine dinucleotide phosphate oxidase, and the inhibition of adipokines[210, 211]. Fructose is the only sugar that leads to a rise in serum uric acid levels, and it does so rapidly via activation of the fructokinase pathway in hepatocytes[212, 213]. In addition, fructose may increase reabsorption of salt and water in the small

intestine and kidney of Wistar-Kyoto rats, which has a synergistic effect in the development of hypertension[214].

Consumption of added sugars may contribute to a higher risk of other MetS components in part by their ability to induce weight gain, but an independent effect is also noticed with short–term feeding trials[112]. The high amounts of rapidly absorbable carbohydrates such as sucrose or HFCS in SSB[215], coupled with the large quantities often consumed, contributes to a high dietary GL, which may stimulate appetite, promote weight gain and lead to glucose intolerance and insulin resistance[88, 216–218]. In addition, the increase in GL could also exacerbate levels of inflammatory biomarkers such as C–reactive protein linked to a higher risk of T2DM and CVD[218]. Also, the caramel coloring used in SSB (especially cola) is high in advanced glycation end products, which may further increase the risk of insulin resistance[219]. Compared with glucose, fructose from sucrose or HFCS has particularly adverse effects on elevating BP through hyperuricemia[164, 220, 221] and raised hepatic de novo lipogenesis (including dyslipidemia, ectopic fat deposition and accumulation of visceral adiposity)[122, 192, 217]. In addition, more and more evidence has shown that when used to replace dietary fats, carbohydrates can lead to reduced HDL–C and elevation of plasma triglyceride[51, 222, 223].

2.5 Summary

Over the past 30 years, total energy intake has increased by an average of 150 to 300 kilocalories per day, and around 50% of this raise comes from liquid energy (primarily SSB)[224, 225]. With the exception of the extremely physically active, very few children or adolescents are able to meet their nutrient needs with room in their diet for many extra energy intakes from added sugars[39]. Given the high consumption of added sugars among youth and the potential for long–term health risks associated with early dietary habits from childhood, it is important to understand the impact of this dietary trend.

Differences in study design, population studied, duration of studies, methodologies of exposure and outcome assessment, data quality and statistical analyses may have contributed to the inconsistent findings[92, 112, 226]. Firstly, cross–sectional studies are not optimal considering its relative weak capability for confounding adjustment and potential reverse causation. Intervention trials are not well suited to capture long-term diet-health patterns since they could be widely affected by the effectiveness of intervention (intensity and potential blindness) and could also be limited by participants' compliance which usually tends to wane with an increasing duration, but they do provide important insight into potential underlying biological mechanisms and help to establish cause-and-effect relationship; also considering ethical issues, intervention trials are generally only performed in adults. Considering sufficient time is required for disease initiation and detection to occur[112], prospective cohort studies with large sample size, long duration and robust measurements would tend to provide the most robust evidence[122], which also enables studying changes over time in added sugar consumption and metabolic indicators while accounting for growth and maturation[174]. However, residual and unmeasured confounding is still possible despite extensive control for many important covariates, particularly when the population is heterogeneous between groups[174].

Secondly, most studies chose to adjust for potential confounding, such as lifestyle factors, and majority of them reported a positive association, suggesting an independent effect of added sugars. Studies that do not adjust for total energy intake in regression analyses tend to yield stronger associations with adiposity measures. Because adjustment for total energy is equivalent to removing effect of drinking SSBs on body weight through the increased energy intake and may thus attenuate the association[157]. Still, a number of studies still reported positive associations with MetS components, even after adjustment for total energy intake and adiposity indicators, supporting the effect of added sugars is not mediated through energy intake or adiposity. However, residual confounding by unmeasured or imperfectly measured factors is inevitable[112]. Higher consumption

of added sugars could be a marker of an unhealthy dietary and/or lifestyle habits[227] that are related to energy balance. Some studies also find sex–related differences in the associations between added sugar consumption and MetS components, it is essential to assess and adjust for pubertal status[165]. Therefore, incomplete adjustment for potential confounders could lead to an improper estimation of the actual associations[112]. The relatively small sample size could be somewhat offset by the use of precise measures and control for various covariates[47]. Nevertheless, the consistent results from different cohorts reduces the likelihood that residual confounding is responsible for the findings[112].

Thirdly, the dietary assessment methods used to evaluate beverage consumption are also important, because each method has its own intrinsic limitations which could influence the effect estimation[92]. In addition, because the relation between added sugar intake and health outcomes is longitudinal, a tool that can assess long–term intake patterns over time, would be more appropriate[228]. Some studies used food frequency questionnaire (FFQ) to collect dietary information and only reported the frequency of consumption, not the absolute intake amount. The potential unclear definition of portion sizes in FFQ may influence the accurate estimate of food and nutrient intake. Short–term dietary recall may not reflect usual intake and may depend on memory, while recalls reported or assisted by parents/guardians may misreport the actual intakes. Foods considered as unhealthy or high in added sugars are under–reported more frequently[229, 230], particularly among overweight subjects[231]. In addition, the potential systematic underreporting of added sugar intake could actually weaken its association with metabolic health outcomes. Several steps could be used to enhance the accuracy of dietary information collected, such as following the multiple–pass method, involving well–trained dieticians, and evaluating the plausibility of energy intake by participants' body weight.

Randomized trials of nutritionist–guided behavioral interventions show that diet change can be accomplished and is associated with beneficial metabolic health

outcomes[40]. The combined evidence from previous studies suggests that reducing consumption of added sugars, especially from SSB, should be considered as a critical dietary approach to reducing CVD risk in youth. Considering the evidence of between added sugar consumption and metabolic health outcomes are still inconclusive among youth, particularly with limited evidence from solid added sugars, more high–quality research with long duration, large representative sample and robust measurements is warranted.

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CHAPTER 3. GENERAL METHODS

3.1 Study Design

3.1.1 Overall design

This dissertation was designed to identify two food sources of added sugars (liquid and solid) in children's daily dietary intake and to provide further evidence on the influence of added sugar consumption from not only liquid, but also solid sources on overall diet quality and to explore its associations (both cross–sectional and longitudinal) with adiposity and MetS components among children at risk of obesity. Since this thesis was not designed to examine the prevalence or risk of MetS among youth, cut-off values of MetS components were not used. The three manuscripts in this dissertation were secondary analyses of data from the QUébec Adipose and Lifestyle InvesTigation in Youth (QUALITY) study, an ongoing prospective cohort investigation.

3.1.2 QUALITY cohort study

3.1.2.1 Recruitment

The QUALITY cohort used a school–based sampling strategy to identify potential participants[1]. About 400,000 recruitment flyers were distributed over 3 consecutive years to parents of children in Grades 2–5, in 1,040 primary schools situated within 75 km of Montreal, Quebec City and Sherbrooke in the province of Québec, Canada. Families interested in participating were invited to contact the research coordinator for additional information, to confirm eligibility and to set an appointment with the research team.

Of 3,350 families who contacted the coordinator, 1,320 families met the inclusion criteria. A total of 634 families including one child and two biological parents participated in the baseline visit. Baseline data collection, when youth were aged 8 to 10 years (Visit 1), was completed between September 2005 and December 2008. The first follow–up, when youth were aged 10 to 12 years (Visit 2), was completed between September 2008 and March 2011. Four families were removed from the cohort following Visit 1 because the child and/or parents did

not complete most or all of the baseline data collection although they initially provided consent. Of the original cohort, 89% (n = 564) completed Visit 2. The QUALITY cohort was not intended to be representative of the Québec population of families with children aged 8 to 10 years.

3.1.2.2 Inclusion criteria

i. Caucasian children of Western European ancestry aged 8 to 10 years (only Caucasian families were recruited to reduce genetic admixture);
ii. With at least one obese biological parent [i.e. body mass index (BMI) > 30 kg/m^2 or waist circumference > 102 cm in men and > 88 cm in women, based on self–reported measurements of height, weight and waist circumference]; and
iii. Both biological parents available to participate in the baseline assessment.

3.1.2.3 Exclusion criteria

i. The mother was pregnant or breastfeeding at the baseline evaluation;
ii. The family had plans to move out of the province;
iii. Children with any of the following
    (i) A previous diagnosis of type 1 or 2 diabetes;
    (ii) A serious illness, psychological condition or cognitive disorder that hindered participation in some or all of the study components;
    (iii) Treatment with anti–hypertensive medication or steroids (except if administered topically or through inhalation); and
    (iv) Following a very restricted diet (< 600 kcal/day).

3.1.2.4 Reasons for non–participation at baseline (Visit 1)

i. Not interested in the study (81%, n = 559);
ii. One biological parent did not participate (11%, n = 76);
iii. Child refused to participate (4%, n = 28);
iv. Lived too far from a study centre (2%, n = 14);
v. Not enough time to participate (1%, n = 7); and

vi. Other (1%, n = 7).

3.1.2.5 Reasons for non–participation at 2–year follow–up (Visit 2)

i. No specific reason (50.0%, n = 33);
ii. Child refuses (most often because of fear of venipuncture, 18.2%, n = 12);
iii. Withdrawal after several missed appointments (9.0%, n = 6);
iv. Family not found (6.0%, n = 4);
v. Family has no time or finds data collection, procedures too long (4.5%, n = 3);
vi. Family moved out of study region (3.0%, n = 2) and
vii. Other (9.0%, n = 6).

3.1.2.6 Ethics

Written informed assent and consent were obtained from all participants and their parents, respectively. The project was approved by the ethics review boards at Centre Hospitalier Universitaire Sainte–Justine and Laval University. Secondary data analysis has been approved by McGill University (REB–III).

3.2 Measurements

Families were followed up every 2 years in a full–day visit at the Unité de recherche clinique du Centre Hospitalier Universitaire Sainte–Justine in Montreal and Hospital Laval in Québec City. Data collection included interviewer–administered questionnaires for children, self–administered questionnaires for parents, biological and physiological measurements for both children and parents.

3.2.1 Anthropometric measures

At each study visit, anthropometric measurements were taken according to standardized protocols[2–4] with children and parents, using a stadiometer for height (while participants standing against a wall and looking straight ahead and then was recorded to the nearest millimeter during maximal inspiration), an electronic scale for weight (while participants wearing light indoor clothing and no shoes

and was measured to the nearest 0.1 kg) and a standard measurement tape for waist circumference (mid–distance between the last floating rib and the iliac crest at the end of a normal expiration). BMI was calculated as weight (kg)/height (m^2) for parents, while the age–and–sex specific BMI percentiles for children were computed using the Center for Disease Control and Prevention (CDC) growth charts[5]. Dual–energy X–ray absorptiometry (DXA)[6] (Prodigy Bone Densitometer System, DF+14664, GE Lunar Corporation, USA) was used to assess fat mass which was converted into a fat mass index (FMI) by dividing fat mass by the square of height (m^2)[7].

3.2.2 Assessment of sexual maturity

The assessment of sexual maturity was made by the pediatrician or by trained nurses using the stages described by Tanner[8, 9], which defined physical measurements of development based on external primary and secondary sex characteristics, such as the size of the breasts, genitalia, testicular volume and development of pubic and axillary hair. It is used to control for differences between children in maturational development not captured in reference growth curves for BMI[10].

3.2.3 Blood pressure

Blood pressure was measured on the right arm with the participants sitting at rest for at least 5 minutes, using an oscillometric instrument (Dinamap XL, model CR9340, Critikon Company, FL, USA)[11]. Five measures were obtained at 1–min intervals and the average of the last three was used in the analyses.

3.2.4 Biochemical analyses

At each clinic visit, blood was obtained from both children and parents by venipuncture after an overnight fast. Samples were centrifuged, aliquotted and stored at –80°C until analysed. Plasma insulin was measured with the ultrasensitive Access immunoassay system (Beckman Coulter, Inc.). Plasma glucose concentrations were determined on the Beckman Coulter Synchron LX20

automat using the glucose oxidase method. All biochemistry analyses for MetS components (including triglycerides, high density lipoprotein–cholesterol (HDL–C) and fasting glucose) were conducted at the Department of Clinical Biochemistry of the Centre Hospitalier Universitaire Sainte–Justine that participated regularly in provincial and international quality control programmes and is accredited by the International Federation of Clinical Chemistry.

3.2.5 Oral glucose tolerance test (OGTT)

A 120–min OGTT was performed in each participant and blood was collected in tubes containing 1 g/L ethylenediaminetetraacetic acid (EDTA) 30, 60, 90, and 120 min after an oral glucose dose of 1.75 g/kg body weight (up to a maximum of 75 g).

Insulin sensitivity (IS) was evaluated using both fasting–based and OGTT–based indices. Fasting insulin (pmol/L) has been identified as a valid method to estimate IS in youth[3]. The homeostatic model assessment of insulin resistance (HOMA–IR), calculated as fasting insulin (mmol/L) × fasting glucose (mmol/L)/22.5[12], has been extensively validated against the hyperinsulinemic–euglycemic clamp, the gold standard method of assessing IS in youth[13, 14]. The Matsuda IS index (Matsuda–ISI) is calculated as 10,000/square root [(fasting glucose × fasting insulin) × (mean OGTT glucose × mean OGTT insulin)][15] and has been validated against the current gold standard method as the best OGTT–based index for estimating IS in youth[13, 16].

3.2.6 Physical activity

Children's physical activity was measured objectively using 7–day accelerometry (Actigraph LS 7164 activity monitor, Actigraph LLC, Pensacola, FL, USA) in the week following the clinic visit[17]. Recordings were excluded when the accelerometer was worn for < 80% of the average time worn on other days. Non–wear time was defined as any period of 60 minutes or more of 0 counts, allowing for one interruption (of 1–min duration) or two consecutive interruptions (2

consecutive minutes)[18]. An interruption was defined as a minute during which count values were > 0 and ≤ 100[19]. Ninety–seven percent of children had more than 4 days 10 hours of accelerometer data and this has been shown to ensure adequate reliability[20]. These accelerometers have been validated in 9 year old children with a correlation (r = 0.58) between mean counts per minute and activity based energy expenditure assessed by doubly–labeled water[21] and the acceleration signals are converted into activity counts (counts/minute)[22].

Measurement quality is ensured by: (i) detailed data collection protocols[23]; (ii) central training of personnel from both study sites and regular monitoring of adherence to the protocol; (iii) verification and calibration of all equipment according to standardized protocols; and (iv) repeat studies conducted to quantify measurement variability and identify its sources.

3.3 Dietary assessment

3.3.1 Protocol for the three 24–hour dietary recalls

The 24–hour dietary recall consists of an interview during which all food and beverages consumed by an individual during the past 24 hours, and the size of their respective portions are evaluated by a trained dietitian. To gather information during the 24–hour recall, the interviewer uses a "multiple pass" method developed by the U.S. Department of Agriculture (USDA) for national nutrition surveys[24]. The interview is divided into three stages: at first step, the respondent is asked to remember and list all foods and beverages consumed during the previous 24 hours, from midnight to midnight; in the second step, details of foods mentioned in the first step are obtained and foods that may have been forgotten are identified; in the last step, the results are reviewed with the respondent. This method has been validated with children 8 to 12 years[25].

Three 24–hour dietary recalls on non–consecutive days including two separate weekdays and one weekend day (the holidays are considered weekend day) were administered over the telephone by a dietitian within 8–12 weeks of Visit 1. The

average of 3–day intakes was calculated in order to reduce intra subject day–to–day variability. Disposable Styrofoam food portion models (i.e. a glass, a bowl, a plate, a plastic spoon and a ruler, etc.) were provided to participants at the clinic visit, along with a short training and practice session. The date and time of the call was not pre–determined as it may influence and change the eating habits of the family during this period. During the call, the dietitian talked alone with the child because the children may have eaten food that they did not want their parents to know about. After speaking with the child, the dietitian would talk with the parent who was in charge of meal preparation to obtain more details on the foods (such as preparation methods and the food brands). Food intake at meals (breakfast, lunch, supper, snacks and other) was also determined. In all, 613 out of 630 participants at baseline and 552 out of 564 participants at 2–y follow–up provided three 24–hour dietary recalls.

3.3.2 Dietary data entry and validation in CANDAT

All food items (n = 2,331) with detailed information (subject code, date of recall, day code, meal code (breakfast, morning snack, lunch, afternoon snack, supper, evening snack and other), food code, unit code and quantity) from three 24–hour recalls in the QUALITY study were entered into the CANDAT nutrient analysis software (Godin London Inc., London, ON, Canada) for validation, calculation and export for further statistical analysis. The nutrient analysis in CANDAT is based on the Canadian Nutrition Files (CNF) 2007b and 2010 (2010 version was used for estimation of added sugars only).

CANDAT has 3 levels of food files: the Master, Institute and User food files. The CNF was used as the Master food file and cannot be edited. The Institute file was established and maintained by copying the food items from the Master file and adding new food items from different research projects in the Research Center of Food Habits of Canadians. The User food file was specifically created to include new food items from the QUALITY project. Identical food codes were used at each level. An extra “0” was added to the end of the original 6–digital code in

CNF to allow the Institute and User Files to fold new food codes into the same code areas as that of the Master food file. This concept of the three–level system allows adding new food items and updating nutritional values for foods to be used for analysis for different projects.

CANDAT is organized and performed in different Modules, which include (1) Food Files Maintenance and Listings (2) Table and Category Definition (3) Subject Files Maintenance and Reports. Specific Tasks within each Module were used to process related information. Task 100 (Food File Maintenance) was used to add new food items from the QUALITY project. Task 200 (Nutrient Table Maintenance) was used to insert values of added sugars and update total sugars with missing values using the latest version of CNF 2010. Task 210 (Food Group Definitions Maintenance) was used to create food groups, such as SSB and FM, by including each unique food code according to the definition. Task 300 (Subject File Maintenance) was used to create and edit all QUALITY subject information and enter 24–hour dietary records. A regularly updated default document in the Research Center of Food Habits of Canadians was used to choose corresponding food code and estimate the portion size, when it is hard to distinguish or unavailable from participants' description. This default document was composed of more than 1,200 food items collected from various research projects and it established standard data entry choices for these foods. Task 310 (Subject File Validation) was used to validate information before being submitted for nutrient analysis. The validation included ensuring each food code actually exists, food unit used is valid and no conflicts between unit codes or meal codes. Each recall was verified by the person who entered it and then double verified by another team member. Every 10^{th} entry was audited by a research dietitian who supervised the staff. Final entries were verified for outlying values to provide a means of catching errors missed during the double verification. Task 330 (Primary Analysis for Nutrient Reports) was used to link all the foods with their nutrients. Task 340 (Secondary Analysis for Nutrient Reports) was used to produce dietary recall

reports of each subject for further statistical analysis (daily intake of nutrients and specific food group, at different meals or days).

3.3.3 Estimation for added sugars values

As the CNF provides data only for total sugars without distinguishing whether it is natural or added, values of added sugars were derived from the USDA Database for the Added Sugars Content of Selected Foods due to the similarity of food description and processing methods between Canada and USA)[26]. In fact 57% of food items in the CNF do not have their total sugar value in the database and all these missing values were completed by manually searching through database from USDA or online resources. Since there is no analytical method for distinguishing between added sugars and naturally occurring sugars, the added sugars values were calculated from sugars listed as label ingredients and nutrient values for total sugars and total carbohydrates for most processed foods. Specific guidelines from USDA[26] for calculating added sugars are listed in the Appendix 1.

If a food item was listed in the USDA database and the total sugar value was the same as that found in the CNF, the value of added sugars was recorded without modification. If an exact or similar item was in the USDA database, but the value of total sugars differed from the CNF, the value of total sugars from the CNF was retained and the value of added sugars from the USDA database was modified using the formula: added sugars = [added sugars (USDA database) × total sugars (CNF)]/total sugars (USDA database). For foods with missing total sugar values, Nutrient Facts labels found on the manufacturer's websites were used. For items without Nutrition Facts labels, such as fresh product and dried spices, the total sugar values were imputed from similar food items in the CNF. When estimation for added sugar values was obtained for all foods, they were entered into CANDAT for each food item.

3.3.4 Creation of food groups for liquid and solid sources of added sugars

According to the liquid and solid sources of added sugars, all food items (n = 2,331) were categorized under 24 groups, based on the food group codes in the CNF (Appendix 2). Each unique food code was entered into a corresponding food category. The solid sources were composed of subgroups as below: dairy and egg products; spices and herbs; fats and oils; poultry products; soups, sauces and gravies; sausages and luncheon meats; ready–to–eat cereals; fruits; pork products; vegetables and vegetable products; nuts and seeds; beef products; fish and shellfish products; legumes and legume products; lamb, veal and game; baked products; sweets; cereals, grains and pasta; fast foods; mixed dishes; and other snack foods. The liquid sources included beverages (only the subgroup of sugar–sweetened beverages (SSB) containing added sugar) and dairy products (only the subgroup of flavoured milk (FM) containing added sugars). Added sugars from solid sources were calculated as total added sugars minus added sugars from liquid sources.

3.3.5 Evaluation of overall diet quality

Several different types of methodologies have been proposed to define healthy diet. The factor and cluster analyses[27] identify food consumption patterns (e.g. similar food intake among a group of individuals), yet do not allow for comparisons against current dietary recommendations. The dietary quality indices[28] evaluate the combination of various nutrients, food groups in relation to current dietary guidelines and/or specific health outcomes[29, 30]. These indices assess diet quality mainly from 2 aspects: adequacy (to measure the sufficiency in consumption of nutrients and foods) and moderation (to evaluate whether certain nutrients or foods are consumed in excess)[31]. In Canada, several dietary quality indices have been used in both adults[29, 32] and youth[33–35] and the adapted Healthy Eating Index (HEI) from US[36] is one of the most widely used continuous measures to evaluate overall diet quality. The latest version of Canadian Healthy Eating Index (HEI–C (2009))[35] was adapted in terms of conformance to the

updated dietary recommendation *Eating Well with Canada's Food Guide (*EWCFG*)*[37].

The HEI–C included 9 components with a continuous proportional score assigned to each component to reach the maximum score of 100. The 9 components are composed of 4 adequacy components: grains (10 points), vegetables/fruit (20 points), milk and alternatives (10 points), meat (10 points) and 5 moderation components: other foods (10 points), total fat (10 points), saturated fat (10 points), cholesterol (10 points) and variety (10 points)[35]. The average daily intake quantities of these 9 components were calculated for each QUALITY participant (servings for food groups were calculated according to EWCFG and grams for nutrients were calculated using CANDAT). For the adequacy components, the increasing levels of intake means higher scores; whereas for the moderation components, the increasing levels of intake means lower scores. Scores for intake between the minimum (0 point) and maximum standards (10 or 20 points) are scored proportionately according to the scoring scheme (Appendix 3). The component of other foods is partly composed of foods rich in added sugars (but not specifically for SSB and/or FM) or solid fats which contribute excess calories and may displace nutrient–dense foods from the diet[38]. An overall higher score indicates closer conformance with EWCFG (sufficient of adequacy components and not excessive of moderation components) and a "good diet" is defined as HEI–C score $\geq$ 80 points[34].

Besides using Canadian recommendations, usage of HEI–C as a single measurement of die quality rather than numerous indicators individually (such as total energy intake, servings of food groups from a food guide, or nutrient intake in relation to current recommendations) provides various statistical advantages[29].

3.3.6 Adjustment for total energy intake

In a population of free–living humans, variation in total energy intake is due largely to physical activity, differences in body size and energy efficiency. Thus,

total energy intake can confound associations with specific nutrients if any of these factors are associated with disease risk[39]. In addition, extraneous variation caused by these factors can weaken associations if the variation resulting from total energy intake is not removed. Analyses to evaluate the relation between dietary composition (i.e. added sugars) and disease risk should be based on an isoenergetic principle[39]. Most nutrients (especially macronutrients) are associated with total energy intake, either because they contribute directly to energy intake, or because individuals who consume more total energy also have a higher intake of all nutrients on average.

The nutrient density approach is one of traditional methods to adjust for total energy intake by expressing as a percentage of energy or as intake per 1000 kcal[39]. This method has several advantages: it can be calculated directly for an individual without the use of any statistical models and it has been used in national dietary guidelines. Beside the nutrient density approach, Willett et al. introduced 4 other multivariate regression models to adjust for total energy intake[39]:

Model 1A (standard multivariate), disease risk = β_1 (nutrient) + α (total energy);
Model 1B (residual nutrient), disease risk = β_1 (nutrient residual) + β_2 (total energy);
Model 1C (energy partition), disease risk = (α + β_1) (nutrient) + α (energy from non–nutrient sources);

Model 2 (multivariate nutrient density), disease risk = β_3 (nutrient density) + β_4 (total energy).

The first three models (Model 1A, 1B, 1C) can be derived from each other, that is, mathematically interconvertible[40–42]. They can all be considered to be different formulations of the same model, with each providing a different perspective on the data. The coefficient β_1 is usually the most relevant coefficient because it

represents the biologically specific effect of the nutrient beyond any effect due simply to its energy content. The coefficient β_1 can also be viewed as representing the "isocaloric" substitution of the nutrient for other sources of energy. Model 1A is widely applied in nutritional epidemiological studies and was thus used in this dissertation for convenient comparison with previous studies.

In general, continuous–variable models are preferred if they fit the data and correspond to likely biological explanations of how dietary factors are related to risk of disease[39]. In this dissertation, all dietary exposure variables (added sugars or SSB) were kept as continuous variables for statistical analysis.

3.4 Statistical analysis

3.4.1 Manuscript 1

This manuscript was set to describe the different sources of added sugars (solid and liquid), to evaluate their influence on youth's nutrition profile and total diet quality and to examine their associations with adiposity indicators.

Considering previous evidence shows different contributions on dietary intake between the two liquid sources of added sugars (SSB and FM), they were thus examined separately in this manuscript. A food group of SSB was created out of the category of "beverages" in the CNF, which included soft drinks, fruit drinks, sports drinks and sweetened tea (but not diet drinks or 100% fruit juice). In addition, a food group of FM was created out of the category of "dairy and egg products" to include ready–to–drink chocolate or other–flavored milks and homemade FM (plain milk to which chocolate flavor powder or syrup was added). Hot chocolate beverages made from hot chocolate powder to which only water had been added were excluded and so were chocolate flavored meal replacements and chocolate milkshakes (these also belong to the liquid sources of added sugars, but they are not regarded as FM, because no milk was added; considering there were only 3 out of 613 children drank in this way with relatively small amounts, it was assumed to have little influence on the analysis of liquid added sugars). Other

rarely used milks or milk replacement products (e.g. goat milk, soy milk beverage) were excluded. Moreover, all 21 subgroups in solid sources of added sugars were studied as a whole group in this manuscript for analysis, considering some subgroups contributed a tiny proportion to solid added sugars.

All QUALITY participants with dietary recalls were categorized into three groups based on the consumption amount tertiles of solid added sugars and tertiles of SSB (tertile was chosen because the lowest quintile or quartile of SSB equals to 0 mL). In addition, considering the relatively low average consumption amount of FM (135 mL over 3 days, with the first and second tertile equal to 0 mL) and potential influence on dietary intakes from the principal liquid added sugars (SSB), eligible QUALITY participants were not categorized into tertiles, but as FM drinkers (those who consumed FM > 0 mL on any one of three–day recalls and did not consume SSB on any day) and non–drinkers (those who did not consume SSB or FM on all three–day recalls).

Distribution of added sugars from solid and liquid sources was described as both % of total added sugars and % of total energy intake. Daily average intake of nutrients (total energy, % of energy from protein, fat and carbohydrate, calcium, phosphorus, potassium, magnesium, zinc, vitamin A, vitamin D), 2 food groups (milk and dairy products, fruit and vegetables) and total HEI–C score was compared among consumption groups of solid added sugars and SSB using one–way analysis of variance (ANOVA), as well as compared between non–drinkers and FM drinkers using an independent t–test. Post–hoc multiple comparisons were performed using Duncan and Dunnett's T3 for equal and unequal variances respectively. Chi–square tests were used to compare the percentage of "good diet" among added sugars groups. The micronutrients (calcium, phosphorus, potassium, magnesium, zinc, vitamin A, vitamin D) were chosen for comparison because they are recently reported with insufficient intakes among Canadian youth[43]. The food group of milk and dairy products was chosen for comparison because it represents a healthy food group and previous evidence shows a potential

replacement by increasing consumption of SSB. The food group of fruit and vegetables was chosen because it is an important component of a healthy diet, which is found to be helpful in preventing chronic disease, independent of its contained anti–oxidant nutrients and fibre[44].

All nutrients and food groups were adjusted for total energy intake and expressed as per 1000 kcal of intake. The analysis was also performed by adjusting for (total energy – energy from added sugars). Multivariate linear regression analyses were used to compare the associations with HEI–C, BMI, BMI Z–score, fat mass and waist circumference (WC) separately for added sugars from solid and liquid sources, after adjustment for age, sex, total energy intake and physical activity (physical activity was not adjusted for HEI–C, because it was generally not regarded as a confounder for diet quality). Missing data were mainly from the records of accelerometers (11% of all participants). No imputation for missing data as they were not randomly missing, since children who were overweight/obese had more missing data. All statistical analyses were conducted using STATA 11.0 (StataCorp LP, College Station, TX, USA). The significance level was set at 5% (two–tailed).

3.4.2 Manuscript 2

A significant positive association between consumption of added sugars from liquid, but not solid sources and adiposity indicators was reported in Manuscript 1. Also previous studies have shown associations between SSB intake and higher risk of MetS components (such as waist circumference, blood pressure, fasting glucose, triglyceride, HDL–C, etc.) in youth[45]. This Manuscript 2 examined whether the relationship between consumption of SSB (the principal component of liquid added sugars) and obesity and other MetS components was more evident in children with higher metabolic risks, such as excess adiposity or impaired glucose tolerance (IGT).

During the preliminary analysis of the data for all participants, multivariate linear regression analyses were used to examine the associations between SSB consumption and individual MetS components. The interaction terms (SSB × overweight status, SSB × glucose tolerance status) were included as covariates in the regression models for different outcome variables. As these interaction terms were statistically significant for several of the outcome measures examined, all further analyses were stratified according to the weight status (BMI < and ≥ 85th percentile) and glucose tolerance status (IGT and normal glucose tolerance). Covariates included age, sex, FMI (for outcomes other than measures of adiposity) and physical activity. Because obesity is considered as one of the most important risk factors for developing MetS and it is often associated with higher consumption of SSB, FMI (an indicator of obesity) was thus adjusted to control its potential confounding with other MetS components. Physical activity (accelerometer) was adjusted as well because it is another common confounder for SSB and MetS components. Although Tanner stage showed some variation, the multivariate linear regression models remained similar with and without adjusting for Tanner stage. The small subgroup of children with IGT (n = 46) also limited the number of covariates, thus Tanner stage was not included in the final model.

Basic characteristics (age, sex, height, weight, WC, FMI, Tanner stage), MetS components (triglycerides, HDL–C, HOMA–IR, systolic blood pressure (SBP)), physical activity and daily dietary intakes were compared using independent t–tests, Chi–square test and Wilcoxon rank–sum test between the subgroups (status of overweight and glucose tolerance) for normally distributed variables, proportions and non–normally distributed variables, respectively. All multivariate regression models were performed with and without adjustment of total energy intake. The β–coefficients were used to describe the changes in the outcome variables associated with each 100 mL increase in SSB intake in BMI and glucose tolerance strata. All statistical analyses were conducted using STATA 11.0

(StataCorp LP, College Station, TX, USA). The significance level was set at 5% (two–tailed).

3.4.3 Manuscript 3

Cross–sectional positive associations between consumption of SSB and higher risk of MetS components (including HOMA–IR) were reported in Manuscript 2. Evidence from previous cross–sectional studies in youth indicate higher consumption of added sugars (primarily in the form of SSB) is linked to impaired glucose homeostasis and insulin resistance, but evidence from longitudinal studies is still lacking. In addition, limited research has been done on the potential health risks with consumption of added sugars from solid sources. This Manuscript 3 examined whether consumption of added sugars is associated with the development of adiposity (2–year changes in fat mass, BMI and WC), impaired glucose homeostasis or insulin resistance (2–year changes in fasting glucose, fasting insulin, HOMA–IR and Matsuda–ISI) and to assess whether associations differ between the two sources (liquid and solid) of added sugars.

Specifically, in Manuscript 2, a more evident association between SSB consumption and MetS components was observed in overweight/obese children and those with IGT. Thus the idea of stratified analysis by weight status was continued to be used in the longitudinal analysis in Manuscript 3 (the stratification by glucose tolerance status was not kept because glucose homeostasis was the main outcome variable). The interaction terms (added sugars × overweight status at baseline) were statistically significant for several outcome variables (fasting glucose and HOMA–IR) in the longitudinal regression models.

Demographic characteristics, weight status and metabolic indicators at baseline and at 2–year follow–up were described for all participants who completed both baseline and follow-up investigations and the two weight–based subgroups (overweight/obese vs. normal–weight subjects at baseline) using proportion and mean (standard deviation). Independent t–tests were used to compare 2–year

changes in outcome variables (FMI, BMI, WC, fasting glucose, fasting insulin, HOMA–IR and Matsuda–ISI) between overweight/obese and normal–weight individuals. In the multivariate linear regression models, 2–year changes in outcome variables were separately examined in all subjects and the two subgroups, adjusting for the baseline value of the outcome variable, as well as age, sex, Tanner stage, energy intake, FMI and physical activity. Socioeconomic status (parents' education and household income) was not adjusted in the regression models, firstly, considering they were not significantly different between two subgroups; secondly, they were not significant in the pilot regression models. All comparisons and regression models were performed among individuals (n = 564) who participated in the investigations at both baseline and 2–year follow–up. This manuscript was not designed to examine the incidence of obesity or other MetS components, therefore no clinical or screening cut-off values were discussed. The β–coefficients were used to describe the 2–year changes in the outcome variables associated with 10 g increase in added sugar intake. All statistical analyses were conducted using STATA 11.0 (StataCorp LP, College Station, TX, USA). The significance level was set at 5% (two–tailed).

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BRIDGE 1

Chapter 2 summarizes evidence from observational studies in youth as well as interventional trials in adults, which suggests associations with higher consumption of added sugars and lower diet quality and higher risk of obesity. However, the majority of these investigations studied added sugars as a whole or only focused on its liquid source of SSB. Considering most added sugars consumed by youth came from solid rather than liquid sources, little is known about whether the influence on youth's dietary intake and association with adiposity indicators are different between added sugars from solid and liquid sources.

The QUALITY study has robust measurement of children's dietary data in three 24–hour recalls, measures of adiposity indicators (i.e., total fat mass by DXA). The food coding in the dietary recall questionnaires enables to create food groups and estimate values of added sugars from both solid and liquid food sources. Moreover, the daily average intake of nutrients and food groups and the HEI–C could be calculated for each participant to evaluate the overall diet quality. All these made it applicable to test the hypotheses in Chapter 4.

CHAPTER 4. MANUSCRIPT 1

Associations between added sugar (solid vs. liquid) intakes, diet quality and adiposity indicators in children at risk of obesity

(This manuscript is under review by *J Acad Nutr Diet*)

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Keywords: added sugars; diet quality; obesity; children; healthy eating index

4.1 Abstract

Background: Few studies in youth assessed the influence of added sugar intake on diet quality and obesity according to the form of its food sources.

Objectives: This study examined the contribution of added sugar (solid vs. liquid) to dietary intake (micronutrient and overall diet quality), and the association between added sugars and adiposity indicators in children at risk of obesity.

Methods: Dietary intake was assessed in three 24–hour recalls in 613 children (8–10 y, with at least one obese parent) in the QUébec Adiposity and Lifestyle InvesTigation in Youth (QUALITY) study. Added sugars were categorized according to sources (solid or liquid (sugar–sweetened beverages (SSB) and flavoured milk (FM)). The Canadian Healthy Eating Index (HEI–C) was used to evaluate overall diet quality. Adiposity indicators included body mass index (BMI) and Z–score, fat mass (dual energy X–ray absorptiometry) and waist circumference (WC). Associations were examined in multivariate linear regression models adjusting for age, sex, energy intake and physical activity (7–day accelerometer).

Results: Added sugars contributed 12% of total energy intake (204 kcal), of which 78% was from solid sources. Higher consumption of solid added sugars was associated with higher total energy, lower intake of micronutrients (phosphorus, potassium, magnesium and zinc), fruits and vegetables, and lower HEI–C scores. A 10 g higher intake of solid added sugars was associated with a 1.3 point lower HEI–C. Referring to liquid added sugars, participants with higher SSB consumption had lower intakes of milk and dairy products and their associated nutrients (calcium, vitamins A & D). A 10 g higher consumption of liquid added sugars was associated with a 2.5 point lower HEI–C, a 0.4 kg/m^2 higher BMI, a 0.1 SD unit higher BMI Z–score, a 0.3 kg higher fat mass and a 0.9 cm greater WC. No association was detected between solid added sugars and adiposity indicators.

Conclusions: Higher consumption of added sugar from SSB and solid sources was associated with lower nutrient density and lower overall diet quality. Positive

associations with adiposity indicators were observed with consumption of added sugars from liquid sources only.

4.2 Introduction

A healthy diet is essential for normal growth in children and adolescents, and helps prevent obesity and related chronic diseases[1]. In recent decades, diets across the world are sweetening, with dramatic increases in the consumption of added sugars[2]. Youth are the highest consumers of added sugars, among whom children aged 9 to 13 years consume the most added sugars – as high as 419 kilocalories per day[3]. Moreover, not all children consume essential nutrients in sufficient quantities. For example, the prevalence of inadequate vitamin A, magnesium, zinc, and phosphorus ranges between 10–30%, and even as high as 67% for calcium in Canadian youth aged 9 to 13 years[4]. In addition, childhood obesity has become a major public health concern around the world. In Canada, 13.1% of children aged 5 to 11 and 10.2% of adolescents aged 12–17 are classified as obese (age and sex–specific body mass index (BMI) $\geq 95^{th}$ percentile)[5].

Although recent U.S. data indicate declines in the consumption of added sugars, the average intake remains high in youth[6]. Added sugars are defined as caloric sweeteners added in the processing or preparation of foods and beverages[7]. More than 60% of daily added sugar intake comes from solid food[8], and the top sources include grain–based desserts, dairy desserts, candies and ready–to–eat cereals[3]. Sugar–sweetened beverages (SSB) are the main liquid source of added sugars in youths' diet in both the U.S. and Canada[9, 10]. Flavored milk (FM) is the other liquid source of added sugars that is particularly popular among school youth. In New York City public schools in 2009, chocolate milk accounted for approximately 60% of total milk purchases[11]. On average, one serving (236 mL, 8 oz) of SSB contains approximately 28 g of added sugars, while the same–sized serving of FM contains 16 g[7].

There is evidence in some[12, 13] but not all[14–17] studies that higher intake of added sugars reduces micronutrient intake, displaces nutrient–dense foods and is associated with obesity and weight gain in youth. Forshee et al., using data from the Continuing Survey of Food Intake by Individuals (1994–1996), reported that the role of added sugars in the diet quality of U.S. children and adolescents is inconsistent and small[15]. In addition, a longitudinal study of 1,203 British children reported no association between SSB consumption at age 5 or 7 y and total fat mass at 9 y[17]. Previous studies relating added sugars to dietary intake and health outcomes generally study added sugars overall or only in liquid form (i.e., SSB and/or FM)[7]. Because most added sugars are from solid sources, the importance of examining their role as well as SSB is recognised in a recent statement by the American Heart Association[7]. The present study investigated the contribution of added sugar intake from solid and liquid food sources (SSB and FM) to overall diet quality in a sample of Canadian children at risk of obesity, and in addition examined the associations between added sugars and adiposity indicators.

4.3 Methods

4.3.1 Study population

This study is a secondary data analysis of 630 children aged 8 to 10 years at baseline participating in the QUébec Adipose and Lifestyle InvesTigation in Youth (QUALITY) study. In all, 613 out of 630 children completed three 24–hour dietary recalls. Methods for this study have been described in detail[18]. These children were at risk of obesity because the recruitment criteria required that at least one biological parent had a BMI $\geq$ 30 kg/m^2 or central obesity (WC > 88 cm for women and > 102 cm for men)[19]. Inclusion criteria for children were no diagnosis of diabetes, not following a very restricted diet (< 600 kcal/day), no regular medications and no serious psychological ailments. Data were collected during a clinic visit followed by telephone contacts. The study was approved by the ethics review boards at Centre Hospitalier Universitaire Sainte–Justine and Laval University. Written informed consent was obtained from parents and assent was obtained from the children.

4.3.2 Dietary assessment

Children's dietary assessment was undertaken on three non–consecutive days of the week, including one weekend day. These were completed by a registered dietitian 8–12 weeks after the clinic visit. Recalls were conducted during telephone interviews. During the clinic visit, children and their parents were given a short training session on the use of a graduated cup and bowl and each participant received a small disposable kit of food portion size models. Interviews were conducted with the child; parents helped with food descriptions and cooking details when necessary.

Because the Canadian Nutrition Files (CNF) provide data on total sugars only without distinguishing whether it is intrinsic to the food or added, the U.S. Department of Agriculture (USDA) Database for the Added Sugars Content of Selected Foods[20] was used as the main data source for added sugars in this study. If differences between the CNF and the USDA Database in the total sugar value were found for the exact or similar food item, the value from the CNF was retained and the added sugar value from the USDA Database was modified using the formula: added sugar = [added sugar (USDA Database) × total sugar (CNF)]/total sugar (USDA Database). If the total sugar value for one food item listed in the CNF and USDA Database was the same, the added sugar value was recorded without modification. For food items with missing total sugars values, the Nutrient Facts labels found on the manufacturer's websites were used. Values of added sugars for each food item were entered into CANDAT nutrient analysis software (version 8.0, Godin London Inc., London, ON, Canada). All further dietary analyses for each participant, including food group creation and nutrient calculation, were undertaken using CANDAT, which bases food composition data on the CNF version 2007b and 2010 (the 2010 version was used for estimation of added sugars only).

All food items were categorized by source of added sugar into 24 groups based on the food group codes in the CNF. Solid sources included added sugar from the

following food groups: dairy and egg products; spices and herbs; fats and oils; poultry products; soups, sauces and gravies; sausages and luncheon meats; ready–to–eat cereals; fruits; pork products; vegetables and vegetable products; nuts and seeds; beef products; fish and shellfish products; legumes and legume products; lamb, veal and game; baked products; sweets; cereals, grains and pasta; fast foods; mixed dishes; and other snack foods. Liquid sources included beverages (by definition, only SSB contains added sugar) and dairy products (by definition, only FM contains added sugars). Added sugars from solid sources were calculated as total added sugars minus added sugars from liquid sources.

A food group for SSB was created from the category "beverages" in the CNF, which included soft drinks, fruit drinks, sports drinks and sweetened tea (but not diet drinks or 100% fruit juice). In addition, a food group for FM was created from the category of "dairy and egg products", which included ready–to–drink chocolate or other–flavored milks and homemade FM (i.e., plain milk to which chocolate flavor powder or syrup was added). Hot chocolate beverages made from hot chocolate powder to which only water was added were excluded, as were chocolate flavored meal replacements and chocolate milkshakes. Other milks or milk replacement products (e.g. goat milk, soy milk beverage) were excluded.

The Healthy Eating Index (HEI) is a measure of overall diet quality that assesses conformance to the *Dietary Guidelines for Americans* (DGA)[21]. In Canada, a similar index of HEI–C (2009)[22] was adapted based on the latest dietary recommendation, *Eating Well with Canada's Food Guide* (EWCFG)[23]. The HEI–C includes 9 components with a continuous score assigned to each component, for a maximum score of 100. The 9 components include 4 adequacy components (i.e., the recommendation for these dietary components is that they should be consumed in sufficient amounts): grains (10 points), fruits and vegetables (20 points), milk and alternatives (10 points), meat and alternatives (10 points) and 5 moderation components (i.e., the recommendation for these dietary components is that intake should be moderate): other foods (10 points), total fat (10 points),

saturated fat (10 points), cholesterol (10 points) and variety (10 points)[22]. For the adequacy components, higher scores indicate higher levels of intake; for the moderation components, lower scores indicate lower levels of intake. Scores for intake between the minimum (0 points) and maximum standards (10 or 20 points) are calculated in proportion to the scoring scheme[22]. An overall higher score (i.e., sufficient for adequacy components and not excessive for moderation components) indicates closer conformity with EWCFG, and a "good diet" is defined as HEI–C score ≥ 80 points[24].

4.3.3 Adiposity indicators assessment

Height measured using a stadiometer with participants standing against a wall and looking straight ahead, was recorded to the nearest millimeter during maximal inspiration. Weight was measured to the nearest 0.1 kg using an electronic scale, with participants wearing light indoor clothing and no shoes. Body mass index (BMI) was calculated as weight (kg)/height (m^2) and age– and sex–specific BMI Z–scores were determined using the growth charts published by the U.S. Centers for Disease Control and Prevention[25]. Dual energy X–ray absorptiometry (DXA) (Prodigy Bone Densitometer System, DF+14664, GE Lunar Corporation, USA) was used to assess fat mass. Fat mass index (FMI) was converted by dividing fat mass by the square of height (m^2)[26]. WC was measured using a standard tape at the mid–distance between the last floating rib and the iliac crest at the end of a normal expiration.

4.3.4 Physical activity assessment

To obtain objective measures of physical activity, children wore a uniaxial activity monitor (Actigraph LLC, Pensacola, Florida) for a 7–day period following the clinic visit. The accelerometer was worn for a mean of 13.4 hours daily and recorded as counts per minute[27]. Consistent with current procedures used by the Canadian Health Measures Survey[28], days were excluded when the accelerometer was worn for less than 10 hours and data from subjects who had worn the accelerometers for less than 4 days was excluded. Ninety–seven percent

of children had more than 4 days of accelerometer data, which has been shown to ensure adequate reliability[29]. Actigraph accelerometers have been validated against activity based energy expenditure assessed by doubly–labeled water in 9 year old children (r = 0.58)[30] .

4.3.5 Statistical analysis

The distribution of added sugars from solid and liquid sources was described as both the % of total added sugars and % of total energy intake. Participants were categorized according to tertile based on the amount of solid added sugars or SSB consumed. Participants were categorized as non–drinkers (who did not consume SSB or FM on any day) or FM drinkers (who consumed FM > 0 mL on at least one of three 24–hour recalls, and did not consume SSB on any day). FM was not categorized into tertile because of low consumption (135 mL averaged over 3 days, with the first and second tertile equal to 0 mL). Daily average intake of nutrients (total energy, % of energy from protein, fat and carbohydrate, calcium, phosphorus, potassium, magnesium, zinc, vitamin A and D), two food groups (milk and dairy products, fruits and vegetables) and total HEI–C scores were compared: (i) across tertile of solid added sugars as well as SSB using one–way analysis of variance (ANOVA); and (ii) between FM drinkers and non–drinkers using an independent t–test. Chi–square tests were used to compare the percentage consuming a "good diet" across added sugar tertile. Post–hoc multiple comparisons were performed using Duncan and Dunnett's T3 for equal and unequal variances respectively. All nutrients and food groups were adjusted for total energy and expressed per 1000 kcal of intake. The analysis was also performed by adjusting for (total energy – energy from added sugars). Multivariate linear regression analyses were used to study the associations between added sugar consumption (10 g) from solid and liquid sources separately, and outcomes of HEI-C, BMI, BMI Z–score, fat mass and WC, after adjustment for age, sex, energy intake and physical activity. Physical activity was not adjusted for in the regression model of HEI–C, because it was generally not regarded as a confounder for diet quality. Due to missing data in several variables,

the final sample size for regression analyses was 613 for HEI-C, 525 for BMI, BMI Z-score and waist circumference and 522 for total fat mass. All statistical analyses were conducted using STATA 11.0 (StataCorp LP, College Station, TX, USA). The significance level was set at 5% (two–tailed).

4.4 Results

QUALITY participants were on average 9.6 y and 54.5% of them were boys. The average values of their BMI z-score was 0.71. They had an average HEI-C score of 75.6 and 38.2% reached the level of "good diet" (data not shown). Their average daily consumption of added sugars was 51 g, which provided 12% of total energy intake (204 kcal). Overall, 78% of added sugars came from solid food – the top four sources were sweets (contributed 29% of added sugars), baked products (25%), ready–to–eat cereal (6%) and other snack foods (4%). The other 22% of added sugars came from liquid sources (SSB and FM) (Table 4.1).

Compared to children in the lowest tertile of solid added sugars (Table 4.2), those in the highest tertile had statistically significantly higher intakes of total energy and % of energy from carbohydrate, as well as lower intakes of % energy from protein, phosphorus, potassium, magnesium and zinc. In addition, higher consumption of solid added sugars was associated with a lower intake of fruits and vegetables, lower total HEI–C scores, and a lower percentage of participants with a "good diet". No statistically significant differences were detected for other nutrients or for milk and dairy products. The results did not change by adjusting for (total energy – energy from added sugars).

Compared to children in the lowest SSB tertile (Table 4.3), those in the highest tertile had statistically significantly higher intakes of total energy and % of energy from carbohydrate, as well as significantly lower intakes of % of energy from protein, calcium, phosphorous, magnesium, zinc, vitamins A and D. In addition, higher consumption of SSB was associated with lower intakes of the two food

groups (milk and dairy products, fruits and vegetables), lower total HEI–C scores and a lower percentage of participants with a "good diet".

Daily dietary intake was compared between non–drinkers and FM drinkers (Table 4.4). FM drinkers had a statistically significantly higher intake of vitamin A and D as well as of milk and dairy products. There was a statistically significantly lower intake of fruits and vegetables in FM drinkers. No statistically significant differences were detected between these two groups for intake of energy, other nutrients or HEI–C.

The multivariate linear regression models (Table 4.5) indicate that consumption of each additional 10 g of added sugars from liquid sources, was associated with a 2.5 point lower HEI–C score, a 0.4 kg/m^2 higher BMI, a 0.1 SD unit higher BMI Z–score, a 0.3 kg greater fat mass and a 0.9 cm higher WC respectively. Each additional 10 g of solid added sugars was associated with a 1.3 point lower HEI–C score. No positive association was detected between solid added sugars and any adiposity indicators.

4.5 Discussion

The present study examined added sugars from both solid and liquid sources in a sample of Canadian children at risk of obesity. The results suggest that higher consumption of solid added sugars and SSB was associated with greater energy intake and lower overall diet quality. Higher consumption of SSB was also associated with lower intake of milk and dairy products (and related nutrients including calcium, vitamins A and D), while FM had little impact on diet with the exception of increasing milk intake and its related nutrients. Positive associations with adiposity indicators were observed with consumption of added sugars from liquid sources only.

The only other study to date that examined different food sources of added sugars and nutrient intake in youth reported that consumption of pre–sweetened cereals

increased the likelihood of children and adolescents reaching Dietary Reference Intakes for the essential shortfall micronutrients calcium, folate, and iron, whereas consumption of SSB, candies, sweets, and sweetened grains decreased the likelihood of meeting the recommended levels for these nutrients[31]. Our study combined all solid sources of added sugars and found that, similar to liquid sources, a higher consumption of solid added sugars was associated with a lower overall diet quality, specifically higher total energy intake and lower % of energy from protein as well as lower intake of micronutrients, fruits and vegetables. While specific food vehicles such as fortified breakfast cereal may contribute positively to overall diet, a small proportion of added sugar came from breakfast cereals in our study.

Our findings are consistent with previous studies[32–36] showing that higher consumption of SSB is linked to higher energy intake, lower consumption of essential micronutrients and lower overall diet quality in youth. A cross–sectional analysis of 1,112 Spanish children aged 6 to 7 years suggested that higher consumption of SSB was associated with higher energy intake, lower consumption of milk, calcium and lower HEI score[35]. Another analysis of dietary data from 7,156 three–day weighed records in 1,069 German youth aged 2 to 19 years found that SSB consumption decreased micronutrient intakes (i.e., calcium and folate) as well as protein intake and total diet quality[34].

When sugars are added to nutrient–dense foods, such as sugar–sweetened dairy products (like FM), youths' diet quality tends to improve[31, 37, 38]. The results of our study were generally in agreement with findings that children aged 5 to 17 years from the USDA Continuing Survey of Food Intakes of Individuals (1994–1998) who consumed FM, drank significantly more total milk and had higher intakes of calcium and phosphorus and higher overall diet quality[37]. Murphy et al. examined 7,557 children and adolescents aged 2 to 18 years from U.S. National Health and Nutrition Examination Survey (NHANES) (1999–2002) and also found that FM drinkers had higher intakes of total milk and micronutrients (i.e.,

calcium, phosphorus, magnesium and potassium) but not higher intakes of added sugars than non–FM drinkers[38].

Studies examining the association between consumption of added sugars and adiposity indicators in youth remain inconclusive. Over the past 10 years, a large number of observational studies including our own findings using QUALITY data[39] report positive associations between liquid added sugar (SSB) consumption and higher risk of adiposity in both youth and adults[7]. However, several recent studies in youth reported negative findings with consumption of SSB or solid added sugars or total added sugars. For example, a recent cross–sectional analyses of 11,181 youth aged 2 to 18 years from NHANES (1999–2004) found that candy consumers were 22% and 26% less likely to be overweight or obese than non–consumers. Nicklas et al.,[40] in an analysis of 3,136 youth aged 6 to 18 years from NHANES (2003–2006), reported no significant associations between intake of total added sugars and adiposity indicators (i.e., BMI Z–score, WC) with adjustment for age, sex, race, total energy intake and physical activity. Our study provides further evidence for a positive association between adiposity and liquid, but not solid added sugars. This may due to a weaker dietary compensation for sugar intake from liquid beverages than for solid food forms of comparable nutrient content[41].

The data for this study used measures of three 24–hour dietary recalls (including one weekend day and two weekdays), several measures of adiposity (including fat mass measured by DXA) and was able to control for physical activity measured by 7–day accelerometry. The food coding in the dietary recall questionnaire enabled us to estimate added sugar values and to create food groups. As a global indicator to evaluate overall diet quality, the HEI–C provided advantages over other methodologies at the population level[42, 43], although it may be limited by the similar weighting factor (10 points) for each component (except for "fruits and vegetables", 20 points)[22]. Although the component of "other foods" (10 points) was partly composed of high-sugar/high-fat foods, this has a very small

contribution of added sugar to the HEI-C score per se. Because the QUALITY cohort study included children at risk of obesity, the results may not be generalizable to the entire population, but it offers the advantage of studying a substantial number of heavier children. Also, the cross–sectional nature of the study means no cause–and–effect relationship could be established.

To date, no specific recommendations have been made on an upper cut–off level for the quantity of added sugars for healthy children. Considering the potential adverse effects of consuming excessive added sugars on micronutrient dilution and health[44], the Beverage Guidance Panel has recommended limiting SSB intake for the general population in the United States[45]. In fact, more than 30 national and subnational governments have made efforts to restrict the availability of SSB in schools[46, 47], including voluntary actions taken by some beverage companies[48]. Per capita intake of milk decreased from 218 to 170 kcal (equivalent as dropped from 605 mL to 472 mL, 2% milk) per day between 1989 and 2008 in U.S. children[49]. Although several recommendations or policies related to the regulation of FM have been announced, no definite agreement has been reached to date. Food and Nutrition Service in the United States published Nutrition Standards for School Meals allowing schools to offer FM if it is fat–free[50]. In addition, Recommended Community Strategies published by the Centers for Disease Control and Prevention require licensed child care facilities in local jurisdictions to ban SSB (including FM)[51], as does the Los Angeles Unified School District Board of Education which has voted to remove FM from schools[52].

In conclusion, higher consumption of added sugars in either solid or liquid form, is linked to a lower diet quality in children, while SSB but not FM further contributes to a lower nutrient dense diet by replacing milk intake. Liquid, but not solid added sugars were positively associated with adiposity indicators, but this was more evident for SSB alone. Further studies are encouraged, especially for solid added sugars, considering that there is still no recommendation specifically for children and adolescents who are the highest consumers of added sugar.

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STATEMENT OF POTENTIAL CONFLICT OF INTEREST:

No potential conflict of interest was reported by the authors.

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Table 4.1 Dietary sources of added sugars among QUALITY[1] study participants at baseline (n = 613)

	g (% of total added sugars)	kcal (% of total energy)
Total Energy	—	1687 (100)
Total added sugars	**51 (100)**	**204 (12)**
Solid sources[2]	**40 (78)**	**160 (9)**
Sweets	15 (29)	60 (4)
Baked products	13 (25)	52 (3)
Ready–to–eat cereal	3 (6)	12 (0.7)
Other snack foods	2 (4)	8 (0.5)
Liquid sources	**11 (22)**	**44 (3)**
SSB[3]	10 (20)	40 (2)
FM[4]	1 (2)	4 (0.2)

[1] QUALITY = QUébec Adiposity and Lifestyle InvesTigation in Youth;

[2] Only top four sources of solid added sugars were listed;

[3] SSB = Sugar–sweetened beverages;

[4] FM = Flavoured milk.

Table 4.2 Daily nutrient and food intake[1] among QUALITY[2] study participants by tertile of added sugar consumption from solid sources (n = 613)

	Added sugars from solid sources			*P*
	1st tertile	2nd tertile	3rd tertile	
Total added sugars (g)	31.8 (15.4)[a]	47.1 (12.7)[b]	74.4 (24.4)[c]	<0.001
Energy (kcal)	1437 (308)[a]	1654 (306)[b]	1939 (378)[c]	<0.001
% of energy from protein	17.6 (3.9)[c]	15.8 (3.0)[b]	14.3 (2.4)[a]	<0.001
% of energy from fat	32.1 (5.2)	32.0 (5.2)	32.5 (4.4)	0.507
% of energy from carbohydrate	51.5 (6.9)[a]	53.6 (6.1)[b]	54.7 (5.6)[b]	<0.001
Calcium (mg/1000 kcal)	525 (161)[b]	508 (148)[ab]	492 (142)[a]	0.077
Phosphorus (mg/1000 kcal)	673 (136)[c]	648 (129)[b]	611 (121)[a]	<0.001
Potassium (mg/1000 kcal)	1490 (325)[c]	1410 (264)[b]	1271 (245)[a]	<0.001
Magnesium (mg/1000 kcal)	143 (29)[b]	140 (29)[b]	132 (29)[a]	<0.001
Zinc (mg/1000 kcal)	5.7 (1.9)[c]	5.3 (1.7)[b]	4.8 (1.2)[a]	<0.001
Vitamin A (µg/1000 kcal)	193 (96)	197 (93)	201 (80)	0.643
Vitamin D (µg/1000 kcal)	3.7 (2.5)	3.7 (2.4)	3.3 (1.9)	0.128
Milk and dairy products (g/1000 kcal)	178 (124)	173 (120)	163 (105)	0.400
Fruits and vegetables (g/1000 kcal)	269 (138)[c]	243 (121)[b]	199 (106)[a]	<0.001
Total HEI–C[3] score (maximum 100)	78.8 (9.6)[c]	75.6 (10.2)[b]	72.5 (11.1)[a]	<0.001
Good diet (≥ 80 score, %)	50.2[c]	37.2[b]	26.6[a]	<0.001

[1] All numbers are expressed as mean (standard deviation), except for the % for "Good diet";

[2] QUALITY = QUébec Adiposity and Lifestyle InvesTigation in Youth;

[3] HEI–C = Healthy Eating Index – Canada (2009);

[a, b, c] Different superscripts in the same row indicate statistically significant difference among groups using ANOVA ($P < 0.05$) and (a, b, c) are marked from the lowest to the highest value.

Table 4.3 Daily nutrient and food intake[1] among QUALITY[2] study participants by tertile of sugar–sweetened beverage consumption (n = 613)

	Sugar–sweetened beverage (SSB) consumption			*P*
	1st tertile	2nd tertile	3rd tertile	
SSB (mL)	2.8 (9.9)[a]	103 (39)[b]	317 (128)[c]	<0.001
Energy (kcal)	1644 (401)[a]	1633 (366)[a]	1754 (394)[b]	0.003
% energy from protein	16.6 (3.3)[b]	16.2 (3.7)[b]	14.9 (3.1)[a]	<0.001
% energy from total fat	32.3 (5.0)	32.6 (5.2)	31.7 (4.6)	0.232
% energy from carbohydrate	52.5 (5.9)[a]	52.6 (6.9)[a]	54.7 (6.1)[b]	<0.001
Calcium (mg/1000 kcal)	543 (164)[b]	504 (135)[a]	477 (145)[a]	<0.001
Phosphorus (mg/1000 kcal)	682 (142)[b]	635 (116)[a]	614 (124)[a]	<0.001
Potassium (mg/1000 kcal)	1488 (316)[c]	1368 (280)[b]	1311 (255)[a]	<0.001
Magnesium (mg/1000 kcal)	148 (33)[c]	136 (27)[b]	130 (24)[a]	<0.001
Zinc (mg/1000 kcal)	5.6 (1.7)[b]	5.1 (1.7)[a]	5.1 (1.6)[a]	0.006
Vitamin A (µg/1000 kcal)	214 (101)[b]	190 (83)[a]	187 (82)[a]	0.004
Vitamin D (µg/1000 kcal)	3.9 (2.6)[b]	3.6 (2.1)[ab]	3.3 (2.0)[a]	0.023
Milk and dairy products (g/1000 kcal)	199 (132)[b]	165 (104)[a]	148 (105)[a]	<0.001
Fruits and vegetables (g/1000 kcal)	266 (130)[b]	233 (122)[a]	211 (117)[a]	<0.001
Total HEI–C[3] score (maximum 100)	78.1 (9.8)[b]	75.0 (10.4)[a]	73.7 (11.1)[a]	<0.001
Good diet (≥ 80 score, %)	46.9[b]	33.8[a]	34.0[a]	0.007

[1] All numbers are expressed as mean (standard deviation), except for the % for "Good diet";

[2] QUALITY = QUébec Adiposity and Lifestyle InvesTigation in Youth;

[3] HEI–C = Healthy Eating Index – Canada (2009).

[a, b, c] Different superscripts in the same row indicate statistically significant difference among groups using ANOVA ($P < 0.05$) and (a, b, c) are marked from the lowest to the highest value.

Table 4.4 Daily nutrient and food intake[1] among QUALITY[2] study participants according to flavored milk consumption (n = 192)

	Non–drinkers[3] (n = 159)	**FM drinkers[4] (n = 33)**	***P***
Flavoured milk (mL)	0 (0)	154 (135)	<0.001
Energy (kcal)	1628 (409)	1736 (334)	0.156
% of energy from protein	16.8 (3.5)	16.5 (2.8)	0.650
% of energy from total fat	32.2 (4.9)	32.9 (4.9)	0.415
% of energy from carbohydrate	52.5 (5.9)	52.0 (6.2)	0.661
Calcium (mg/1000 kcal)	540 (162)	592 (158)	0.092
Phosphorus (mg/1000 kcal)	684 (143)	708 (121)	0.378
Potassium (mg/1000 kcal)	1510 (321)	1480 (290)	0.616
Magnesium (mg/1000 kcal)	149 (31)	155 (44)	0.464
Zinc (mg/1000 kcal)	5.6 (1.8)	5.3 (1.2)	0.204
Vitamin A (µg/1000 kcal)	208 (94)	255 (123)	0.014
Vitamin D (µg/1000 kcal)	3.7 (2.6)	5.1 (2.9)	0.006
Milk and dairy products (g/1000 kcal)	190 (130)	260 (129)	0.005
Fruits and vegetables (g/1000 kcal)	281 (133)	229 (118)	0.038
Total HEI–C score (maximum 100)	78.5 (9.8)	78.1 (9.8)	0.835
Good diet (≥ 80 score, %)	48.4	51.5	0.747

[1] All numbers are expressed as mean (standard deviation), except for the % for "Good diet";

[2] QUALITY = QUébec Adiposity and Lifestyle InvesTigation in Youth;

[3] Non–drinkers were defined as those who did not consume SSB or FM on any of the three 24–hour recalls;

[4] FM drinkers were defined as participants who consumed FM > 0 mL on any one of the three 24–hour recalls and did not consume SSB on any day;

Table 4.5 Multivariate linear regression analyses of the association between added sugars (liquid vs. solid) and indicators of diet quality and adiposity among QUALITY[1] study participants

Indicators	β–coefficient	*P*
HEI–C[2] (n = 613)[3]		
Solid added sugars (10 g)	–1.28	<0.001
Liquid added sugars (10 g)	–2.52	<0.001
BMI[4] (kg/m^2) (n = 525)		
Solid added sugars (10 g)	–0.18	0.084
Liquid added sugars (10 g)	0.40	0.007
BMI Z–score (n = 525)		
Solid added sugars (10 g)	–0.05	0.079
Liquid added sugars (10 g)	0.08	0.041
Total fat mass (kg) (n = 522)		
Solid added sugars (10 g)	–0.17	0.041
Liquid added sugars (10 g)	0.27	0.025
Waist circumference (cm) (n = 525)		
Solid added sugars (10 g)	–0.55	0.052
Liquid added sugars (10 g)	0.87	0.035

[1] QUALITY = QUébec Adiposity and Lifestyle InvesTigation in Youth;

[2] HEI–C = Healthy Eating Index – Canada (2009);

[3] Due to missing data, the final number of participants in the regression models is listed in the bracket.

[4] BMI = Body mass index;

Covariates included age, sex, energy intake and physical activity (physical activity is not adjusted for in the HEI–C model).

BRIDGE 2

Chapter 2 suggests that higher consumption of total added sugars or SSB is associated with higher risk of adiposity and some other MetS components in youth, but the findings remain inconclusive. Chapter 4 agrees with previous evidence and provides further evidence that added sugars consumed from both solid and liquid sources are associated with higher energy intake and lower diet quality, and only higher intake of liquid, but not solid added sugars is associated with higher risk of adiposity. To date, little is known whether the associations between added sugar consumption and metabolic health outcomes could be modified by excess adiposity or IGT. Considering SSB are the primary component of liquid added sugars, while FM consumption in QUALITY participants was relatively low, only SSB was evaluated in Chapter 5.

The QUALITY dataset is composed of a rich sample of children at risk of obesity and a number of them had IGT. In addition, the robust measurements of three 24–hour recalls, adiposity indicators (e.g., total fat mass, by DXA), glycemic measures (e.g. HOMA–IR), blood pressure, concentrations of triglycerides and HDL–C, and physical activity (by 7–day accelerometers), all which provided a great chance to testify the above hypotheses in Chapter 5.

CHAPTER 5. MANUSCRIPT 2

Adiposity and Glucose Intolerance Exacerbate Components of Metabolic Syndrome in Children Consuming Sugar–Sweetened Beverages: QUALITY Cohort Study

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Running title: Sugar-Sweetened Beverages and Metabolic Syndrome Components

5.1 Abstract

Background Sugar–sweetened beverages (SSB) consumption is linked to weight gain and metabolic syndrome (MetS) components in children, but whether these associations are modified by excess weight and glucose tolerance status in children is not known.

Objective To examine the cross–sectional associations between SSB intake and MetS components among children above and below the 85th BMI percentile and those with and without impaired glucose tolerance (IGT).

Methods Data were from the QUébec Adiposity and Lifestyle InvesTigation in Youth (QUALITY) study (2005–2008). Caucasian children aged 8–10 years (n = 630) were recruited from 1,040 primary schools in Québec, Canada. SSB consumption was assessed by three 24–hour dietary recalls, body fat mass by dual–energy X-ray absorptiometry, physical activity by 7–day accelerometer. Multivariate linear regressions were used, with age, sex, fat mass index and physical activity as covariates, including waist circumference (WC), systolic blood pressure (SBP), concentrations of triglyceride and high–density lipoprotein cholesterol and homeostasis model assessment of insulin resistance (HOMA–IR) as outcome variables.

Results Among overweight children, a 100 mL higher SSB consumption was associated with 0.10 unit higher HOMA–IR ($P = 0.009$) and a 1.11 mm Hg higher SBP ($P = 0.001$). In children with IGT, a 100 mL higher SSB consumption was associated with 1.44 mm Hg higher SBP and 4.04 cm higher WC ($P < 0.001$). These associations were not observed among children <85th BMI percentile.

Conclusions Our results suggest that the association between higher SSB consumption and MetS components is more evident in overweight/obese and glucose intolerant children.

What is already known about this subject:

1. The increase in sugar–sweetened beverage (SSB) consumption over the last generation is temporally associated with epidemic levels of childhood obesity;
2. There is increasing evidence linking sugar consumption to the development of metabolic syndrome and type 2 diabetes.

What this study adds:

1. Higher SSB consumption is associated with elevated systolic blood pressure and greater insulin resistance among overweight/obese children whereas these associations are not evident among normal–weight children;
2. In youth with impaired glucose tolerance, higher SSB consumption is strongly associated with greater adiposity.

5.2 Introduction

In the past 3 decades, there has been a tripling in the prevalence of childhood obesity coincident with a rising prevalence of insulin resistance and metabolic syndrome (MetS)[1–3]. In the US National Health and Nutrition Examination Survey (NHANES, 1999–2002), the prevalence of MetS was 1.1 and 26.2 percent among normal–weight and overweight adolescents, respectively[3]. According to the US National Cholesterol Education Program Adult Treatment Panel III (NCEP/ATP III)[4], clinical identification of MetS requires any three of the five following components: abdominal adiposity, hypertension, dysglycemia, high plasma triglycerides and low high–density lipoprotein cholesterol (HDL–C). Data from NHANES (1999–2002) indicate that the prevalence of impaired fasting glucose in the US adolescent population reached 2.75 million[5] and that it is highly prevalent among adolescents who are overweight or obese[6, 7].

A notable dietary change corresponding with the increased incidence of obesity and insulin resistance is the increase in the consumption of added sugar, mostly in the form of sugar– sweetened beverages (SSB)[8, 9]. SSBs include the full spectrum of soft drinks, fruit drinks, energy and vitamin water drinks (but not diet drinks,

flavored milks or 100% fruit juice)[10]. Results from two U.S. National Health and Nutrition Examination Survey (NHANES 1988–1994, 1999–2004) among children and adolescents (2–19 y) indicated that overall per–capital daily energy contribution from SSB reached 224 kcal/day and the largest increases occurred among children aged 6 to 11 years[11]. The increasing intake of SSB over milk in children's diets has a negative effect on their dietary quality[12–14].

There are numerous studies reporting associations between SSB intakes and adverse health conditions in adults; excess weight gain[15–17], type 2 diabetes[10, 17, 18] and MetS[18]. Similar associations between SSB consumption and metabolic health outcomes were also observed among children and adolescents during the past 10 years. The first prospective study of 548 school children (11.7 ± 0.8 y) found that SSB consumption at baseline was independently associated with an increase in body mass index (BMI, mean 0.18 kg/m^2 for each daily serving, $P = 0.02$)[19]. In addition, an analysis of 6,967 US adolescents (12–19 y) from NHANES data (1999–2004) indicated that each additional serving of SSB intake was associated with a number of MetS components (a 0.47 cm increase in waist circumference, $P < 0.001$; a 0.16 mm Hg increase in systolic blood pressure, $P = 0.03$; a 0.01 mmol/L decrease in HDL–C, $P < 0.001$ and a 5% increase in HOMA–IR, $P = 0.01$; but not with triglycerides)[20]. However, not all studies in youth[21, 22] or adults [23] show such associations.

There are some limited indications from both animal and human studies that excess adiposity or insulin resistance may modulate the metabolic response to carbohydrate and more specifically to SSB intake. Hininger–Favier et al. fed a high–fructose diet to insulin–resistant Wistar rats for 6 weeks and observed an increase in blood glucose, triglycerides and plasma insulin[24], whereas in a similar study with non–insulin–resistant Wistar rats, these metabolic consequences in relation to the same high–fructose diet were of much lower magnitude[25]. A cohort study of children (2–3 y) found that among those overweight children (BMI 85th – 95th percentile) at baseline who consumed a parent–defined serving ≥ 3 SSB/day

were nearly 2.0 times (95% CI: 1.1–2.8) as likely to remain overweight compared to those consuming <1 SSB/day after one year follow–up, while among children who had BMI <85th percentile, no such association with SSB consumption was observed[26]. In addition, in a small study of exclusively overweight children (n = 95, 9–11 y), SSB consumption was linked to higher triglycerides but not insulin sensitivity (measured by HOMA–IR)[27]. These studies all suggest that the use of carbohydrates by the body may well be altered by weight status or glucose tolerance status.

This study set out to examine the relationship between SSB consumption and MetS components in a cohort of children at high risk of overweight and to test if the associations were modified by excess adiposity or impaired glucose tolerance (IGT).

5.3 Methods

5.3.1 Study population

The project was approved by the ethics review boards at Centre Hospitalier Universitaire Sainte–Justine and Laval University, and written informed consent and assent were obtained from parents and children, respectively. Participants were 630 children aged 8–10 years recruited in the QUébec Adipose and Lifestyle InvesTigation in Youth (QUALITY) study. The methods for this study have been described in detail elsewhere[28]. Briefly, these children were at risk of obesity because, by design, at least one biological parent had a (BMI ≥ 30 kg/m^2) or central obesity (waist circumference >88 cm for women and >102 cm for men), and children of obese parents are known to be at higher risk[29]. Participants were recruited between 2005 and 2008 through public and private primary schools using pamphlets distributed to all children in grades 2–5 in schools located within 75 km of Montréal, Québec City and Sherbrooke in the province of Québec, Canada. The pamphlet invited parents to contact the study center if they met the inclusion criteria. For families that expressed interest, screening for eligibility was conducted in a structured telephone interview using pre–selection criteria.

Children with any of the following criteria were excluded: a previous diagnosis of diabetes; presenting with a serious condition that hindered participation in the study; being treated with anti–hypertensive; or consuming a diet less than 600 kcal/day. Recruitment into the study was limited to Caucasian families due to genetic analyses undertaken in the QUALITY study. Due to missing data among some participants, the final sample sizes for the regressions were 543 and 539 for the stratification by 85th BMI percentile and glucose tolerance status, respectively.

5.3.2 Pubertal status, anthropometry and body composition assessment

Pubertal status was scored by trained nurses according to Tanner[30, 31]. Height was measured with a stadiometer with participants standing against a wall while looking forward. Height was recorded to the nearest 0.1 cm during maximal inspiration. Weight was measured to the nearest 0.1 kg, with an electronic scale, with participants wearing light indoor clothing and no shoes. Age and sex percentiles for BMI were computed using a SAS program for the 2000 CDC growth charts[32]. Waist circumference was measured at the middle point between the iliac crest and the lowest rib with participants standing straight up and wearing a hospital gown. Dual–energy X–ray absorptiometry (DXA) (Prodigy Bone Densitometer System, DF+14664, GE Lunar Corporation, USA) was used to assess fat mass, which has been found to be highly reliable for body composition assessment in children[33]. Then it was converted into a fat mass index (FMI) by dividing fat mass by the square of height (m^2)[34].

5.3.3 Biochemical and blood pressure measurements

Blood was obtained by venipuncture after an overnight fast and placed in 1g/L EDTA collection tubes kept on ice until centrifugation. Plasma was separated on site within 20 minutes of collection, frozen on dry ice, and stored at –80 °C until analysis. An oral glucose tolerance test was performed and blood was collected 120 min after an oral glucose dose of 1.75 g/kg body weight (up to a maximum of 75 g). Children with 2 h post load plasma glucose $\geq$ 140.5 mg/dL (7.8 mmol/L) were classified as impaired glucose tolerance[35]. Homeostasis model assessment of

insulin resistance (HOMA–IR) was calculated from fasting plasma glucose and insulin according to Matthews' formula[36]. Higher HOMA–IR values indicate lower insulin sensitivity. Glucose, HDL–C, and triglycerides were measured using a Synchron LX®20 (Beckman Coulter). Plasma insulin was measured using an ACCESS® 2 immunoassay (Beckman Coulter) with no cross–reactivity with pro–insulin or C–peptide. Blood pressure was assessed with participants in the sitting position using an oscillometric instrument (Dinamap XL, model CR9340, Critikon Company, FL, USA). Five measures were obtained at one–minute intervals and the average of the last three was used in the analyses.

5.3.4 Physical activity assessment

To assess physical activity, children wore a uniaxial accelerometer (Actigraph LS 7164 activity monitor, Actigraph LLC, Pensacola, FL, USA) for a 7–day period in the week following the clinic visit. Of the 560 children with accelerometer data, 97% had more than 4 days of data, which has been shown to ensure adequate reliability[37]. In both sexes, the mean number of hours that the accelerometer was worn daily was 13.4 hours. Accelerometer output is in the form of 'counts' which is a unitless recording of acceleration[38].

5.3.5 Dietary assessment

Children's dietary assessment was based on three 24–hour dietary recalls recorded by a dietitian within 8 weeks of the clinic visit, on non–consecutive days of the week including one weekend day. In order to minimize the burden to families, recalls were conducted by telephone. At the clinic visit, both the children and their parents were given a short training session on the use of a graduated cup, bowl and other portion size models. Each participant then received a small disposable kit of food portion size models to take home. The interview was done with the children and one parent was involved to help with food description where needed. Telephone interviews for the 24–hour dietary recalls have been validated in youth with good results[39]. In the analysis a food group was created for SSB which included soft drinks, fruit drinks, sports drinks and sweetened tea. The nutrient

analysis of the dietary data was completed using the CANDAT software, version 2007 (Godin London Inc., London, Ontario, Canada), of which the food composition data is based on 2007b Canadian Nutrient File.

5.3.6 Statistical analysis

During the preliminary analysis of the data for all participants, multivariate linear regression analyses were used to examine the associations between SSB consumption and individual MetS components. Covariates included age, sex, FMI (for outcomes other than measures of adiposity) and physical activity. The interaction terms (SSB × overweight status, SSB × glucose tolerance status) were included as covariates in the regression models for the different outcome variables. As these interaction terms were statistically significant for several of the outcome measures examined, all further analyses were stratified according to the overweight status (BMI < and ≥ 85^{th} percentile) and glucose tolerance status. Independent *t* tests, χ^2 test and Wilcoxon rank–sum test were used to examine the characteristics of participant between BMI and glucose tolerance categories for normally distributed variables, proportions and non–normally distributed variables, respectively. All statistical analyses were conducted using STATA 11.0 (StataCorp LP, College Station, TX, USA). The significance level was set at 5%.

5.4 Results

Selected characteristics of participants are shown in Table 5.1. Children who were ≥ 85^{th} BMI percentile and children with IGT were older, more likely above Tanner stage 1, less physically active (accelerometer), with excess adiposity (higher waist circumference and FMI) and with worse levels of MetS components (higher triglyceride levels, HOMA–IR, systolic blood pressure and lower HDL–C) than children who were < 85^{th} BMI percentile or who did not have IGT.

Intakes of energy, three major macronutrients, and SSB are shown in Table 5.2 by weight group and by IGT status. More overweight children consumed SSB on at least one of the three days of recorded intake (overweight vs. normal–weight

group, 70.8% vs. 62.6%) ($P = 0.035$), but otherwise there were no differences in reported nutrient intake between these groups. The median daily intake of SSB among SSB consumers was 146 mL, with the interquartile range of 170 mL. Multivariate linear regression analyses for the different outcome variables for all participants are summarized in Table 5.3. These overall results indicated that a higher consumption of 100 mL SSB was associated with a 0.58 mm Hg higher systolic blood pressure ($P = 0.008$) and an increase of 0.28 kg/m^2 BMI ($P = 0.025$). No significant associations were found for other MetS components. The interaction terms for SSB × BMI category and SSB × IGT indicated significant interactions for the following outcomes; SSB × BMI 85th percentile for HOMA–IR, $P = 0.002$ and systolic blood pressure, $P = 0.033$; SSB × IGT for waist circumference, $P < 0.001$). Given these interactions with weight status and glycemic status, further analyses were stratified by BMI and IGT groups. Multivariate linear regressions using different MetS components as dependent variables while stratifying by the 85th BMI percentile cutoff are summarized in Table 5.4. Among overweight children (≥ 85th BMI percentile), a 100 mL increase in SSB consumption was associated with 0.10 unit higher HOMA–IR ($P = 0.009$), after controlling for age, sex, FMI and physical activity. In addition, a 100 mL higher intake of SSB was associated with a 1.11 mm Hg higher systolic blood pressure ($P = 0.001$), after controlling for sex, height, FMI and physical activity. No significant associations were observed between SSB intake and MetS components in children who were below the 85th BMI percentile.

Multivariate linear regressions using different MetS components as dependent variables while stratifying by glycemic status are summarized in Table 5.5. In children with IGT, a 100 mL higher SSB consumption was associated with a 1.44 mm Hg higher systolic blood pressure ($P = 0.048$). Regression models for systolic blood pressure included the covariates listed above plus height but did not include age given the constraints with the number of independent variables that could be used in the smaller subset of children with IGT (n = 46). Among children with IGT, significant positive associations were observed with several measures of

adiposity. For example, a 100 mL higher SSB consumption was associated with a 4.04 cm higher waist circumference ($P < 0.001$), after controlling for age, sex and physical activity. Similar to waist circumference, a 100 mL higher SSB consumption was associated with a 1.12 kg/m^2 higher FMI as determined by DXA ($P < 0.001$). While SSB intake did not account for a high proportion of the variance explained in some models, it contributed to 25% and 27% respectively for the variance of waist circumference and FMI in the regression model among children with IGT (data not shown). Among children with normal glucose tolerance, a 100 mL higher SSB consumption was associated with 0.49 mm Hg higher SBP ($P = 0.033$), but no other associations of SSB intake with MetS components were observed.

The associations between SSB and MetS components persisted after controlling for total energy intake suggesting that SSB intake may have an independent effect on MetS components in children (Table 5.3, 5.4 and 5.5). To assess the robustness of the findings, sensitivity analyses were conducted by stratifying children by the 95th BMI percentile or the median value of HOMA–IR and the same relationships between SSB intake and MetS components were observed. In addition, as pubertal development is associated with insulin resistance[40], Tanner stage was included in sensitivity analyses and it did not change the results.

5.5 Discussion

This study suggests that overweight or glucose intolerant children are more likely to experience deleterious metabolic effects associated with SSB consumption compared with normal–weight children or children without IGT. Among heavier children, SSB intake was associated with both higher HOMA–IR and higher systolic blood pressure. Additionally among those children with IGT, SSB consumption was associated with higher systolic blood pressure and greater adiposity as measured by both waist circumference and fat mass index.

Evidence from both observational and interventional studies support an association between SSB consumption and weight gain in both children and adults[19, 26, 41–43]. Analysis of a prospective study which included 16,771 children (9–14 y) indicated that children consuming an increased intake by ≥ 2 serving/d of SSB from the prior year gained more weight (+ 0.10 kg/m^2, $P = 0.01$) than those with unchanged intake[44] . A cross–sectional study of 5,033 boys (10–19 y) found that waist circumference and BMI were positively associated with a one–serving higher intake of SSB (+0.09 cm, +0.10 kg/m^2 respectively, $P < 0.001$)[14]. Consistent with the above studies, our study found there was a positive association between SSB intake and BMI among all participants. In our analysis stratified by IGT status, however, we found that among children with IGT, SSB was strongly associated with waist circumference and fat mass index, but this was not the case for those children without IGT. In contrast, among studies of British children (5–7 y at baseline)[21] and Portuguese children (5–10 y)[22], no association between SSB intake and higher risk of overweight or fat mass was observed. These negative findings are possibly due to very low SSB consumption[21] or the under–reporting in parental recall of their children's food intakes[22].

The association between high SSB intake and higher blood pressure is supported by several studies in adults[45–47] and one in adolescents[48]. Among adolescents (12–18 y) from NHANES (1999–2004), higher systolic blood pressure was associated with higher consumption of SSB[48]. Data from the Nurses' Health Study which followed 155,594 US women free of physician–diagnosed hypertension for 12 years indicated a strong positive association between SSB intake and an increased risk of hypertension (≥ 4 servings/d vs. < 1 serving/d, age–adjusted relative risk 1.60, $P < 0.001$)[49]. In a clinical study, administration of 200 g of fructose daily for 2 weeks to healthy adult men resulted in significant increases in both systolic (7 ± 2 mm Hg, $P < 0.004$) and diastolic (5 ± 2 mm Hg, $P < 0.007$) blood pressure[50]. In an 18–month intervention trial, a serving/day reduction in SSB was associated with a 1.8 mm Hg (95% CI 1.2 to 2.4) reduction in systolic blood pressure after controlling for BMI[51]. To our knowledge, there are only two studies that suggest

that fructose intake does not influence the risk of developing hypertension, but the data are from self–reported hypertension[23, 52].

Insulin resistance which is found among a large number of overweight adolescents[53] underpins the pathophysiology of MetS. Bremer et al. found that an additional serving of SSB was associated with a 5% increase in HOMA–IR ($P < 0.01$) among US adolescents[20]. This is consistent with an analysis of 2,500 adults from Framingham Offspring Study which showed SSB consumption (≥ 2 serving/d vs. none) was positively associated with HOMA–IR (+ 0.5 unit, $P = 0.004$) after adjusting for BMI[54]. The results in our study indicated a significant association between higher SSB consumption and greater HOMA–IR among overweight children, which is also in accord with the mounting evidence to support the relationship between excess SSB intake and decreasing insulin sensitivity[52] and higher incidence of type 2 diabetes[41, 55, 56].

The strengths of this study include robust measures of body composition by dual–energy x–ray absorptiometry and physical activity by accelerometry. However, since this is a cross–sectional study of SSB consumption and MetS components, we are unable to determine the direction of these associations. In addition, we saw no difference between children who were and were not overweight in terms of total reported energy intake. The heavier children did have less physical activity and may have also under–reported their food intake or may have reduced their intake as they had just entered a clinical study. The under–reporting issues are commonly documented in self–reports of dietary intakes among both youth and adult populations[57, 58]. Specific food items particularly foods rich in fat and/or carbohydrate (such as SSB) are more frequently underestimated during the dietary recalls[59, 60]. It is also found that under–reporting increases with body mass index but underestimation of energy intake is not confined to overweight subjects[61, 62]. Finally, the diet was only measured for 3 days, so the associations between SSB intake and MetS components are likely attenuated by within–person variability in diet[63]. Although we observed a significant proportion of children who did not

report any SSB consumption during the 3–day recalls, this is in agreement with other studies[11]. The SSB intake of our participants was low compared to some studies[11, 14, 44, 64, 65], but similar to a British study of slightly younger children (5–7 y)[21]. Despite these relatively low levels of consumption overall, clear associations were present in our data.

These findings are likely clinically relevant given the observed magnitude of associations between SSB consumption and MetS components. While the differences in systolic blood pressure by SSB intake are not large across all children, the 0.58 mm Hg higher level of BP associated with a 100 mL increase in SSB intake is comparable to a difference of 0.93 mm Hg on average between normal–weight and overweight children, and a difference of 0.95 mm Hg between children with and without IGT. The relationship of SSB intake with waist circumference indicated among glucose intolerant children, a 100 mL higher SSB consumption was associated with a 4.04 cm higher waist circumference. Consistent with a strong association between obesity and SSB consumption, SSB intake accounted for 25% and 27% of the variance in waist circumference FMI, respectively. In adults, an elevated waist circumference is the most prevalent manifestation of MetS and is associated with increased risk of both type 2 diabetes and cardiovascular disease[66]. Taken together, these results suggest that health promotion efforts to curb the growing SSB consumption and further studies to define particularly vulnerable groups are warranted.

5.6 Conclusion

Children who were $\geq 85^{th}$ BMI percentile or glucose intolerant children appear to have a greater susceptibility to the deleterious metabolic effects of SSB than children $< 85^{th}$ BMI percentile or children without impaired glucose tolerance. Thus, children who are metabolically at risk may require targeted dietary advice to limit SSB consumption. This may not only represent a means to treat childhood obesity, but also a means to mitigate the future risk of MetS, type 2 diabetes and cardiovascular disease.

5.7 Conflict of interest statement

No potential conflict of interest was reported by the authors.

5.8 Acknowledgements

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Jiawei Wang and Sean Mark conceived the study design, finished the analysis and interpretation of data and the drafting of the manuscript. Melanie Henderson and Jay Wortman involved in the data interpretation and critical revision of manuscript. Jennifer O'Loughlin and Angelo Tremblay are co–principal investigators of the QUALITY study; they are responsible for acquisition of data and make critical revision of manuscript. Katherine Gray–Donald and Gilles Paradis conceived the study design, involved in the data interpretation and supervision of the whole manuscript. All authors were involved in writing the paper and had final approval of the submitted and published versions.

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Table 5.1 Characteristics of the QUALITY[a] study participants stratified by 85th BMI[b] percentile and glucose tolerance status

Characteristics	< 85th BMI percentile (n = 368)	≥ 85th BMI percentile (n = 264)	*P*	Normal glucose tolerance (n = 555)	Impaired glucose intolerance (n = 49)	*P*
Basic						
Age (years)	9.5 (0.9)[c]	9.7 (0.9)	0.048	9.6 (0.9)	10.0 (0.8)	<0.001
Boys (%)	54.3	54.8	0.936	55.0	49.0	0.456
Height (m)	1.37 (0.08)	1.42 (0.08)	<0.001	1.38 (0.08)	1.42 (0.08)	0.001
Weight (kg)	31.3 (4.9)	47.8 (11.1)	<0.001	37.4 (10.9)	46.1 (14.8)	<0.001
Waist circumference (cm)	59.6 (4.5)	78.5 (10.7)	<0.001	66.7 (11.6)	75.4 (15.2)	<0.001
Fat Mass Index (kg/m^2)	3.2 (1.3)	8.7 (3.0)	<0.001	5.3 (3.3)	7.8 (4.0)	<0.001
Tanner stage > 1 (%)	16.3	29.0	<0.001	20.1	34.7	0.020
Metabolic parameters						
Triglycerides (mmol/L)	0.7 (0.3)	1.0 (0.5)	<0.001	0.8 (0.4)	1.0 (0.5)	0.005
HDL–C[d] (mmol/L)	1.2 (0.3)	1.1 (0.2)	<0.001	1.2 (0.3)	1.1 (0.2)	0.007
HOMA–IR[e]	0.8 (0.4)	1.5 (0.9)	<0.001	1.0 (0.7)	1.8 (1.3)	<0.001
Systolic blood pressure (mm Hg)	92.0 (7.7)	96.3 (8.0)	<0.001	93.2 (7.8)	100.2 (9.0)	<0.001
Physical activity						
Accelerometer (counts/min)	625 (210)	578 (181)	0.005	615 (203)	519 (125)	<0.001

[a]QUALITY = QUébec Adipose and Lifestyle InvesTigation in Youth.

[b]BMI = body mass index.

[c]Mean (Standard Deviation).

[d]HDL–C = high–density lipoprotein cholesterol.

[e]HOMA–IR = homeostatic model of insulin resistance.

Table 5.2 Daily nutrients intakes for of the QUALITY[a] study participants stratified by 85th BMI[b] percentile and glucose tolerance status

Characteristics	< 85th BMI percentile (n = 368)	≥ 85th BMI percentile (n = 264)	*P*	Normal glucose tolerance (n = 555)	Impaired glucose intolerance (n = 49)	*P*
Energy intake (Kcal)	1694 (388)[c]	1678 (402)	0.619	1690 (398)	1653 (340)	0.527
Carbohydrate intake (g)	225 (57)	219 (55)	0.181	223 (57)	214 (46)	0.265
Protein intake (g)	67 (19)	68 (18)	0.537	68 (19)	68 (17)	0.770
Fat intake (g)	61 (18)	61 (19)	0.813	61 (19)	61 (17)	0.856
SSB[d] intake (mL)	67 [0–200][e]	83 [0–198]	0.066	82 [0–200]	81 [0–209]	0.392
Consuming SSB (%)	62.6	70.8	0.035	66.0	67.4	0.844

[a]QUALITY = QUébec Adipose and Lifestyle InvesTigation in Youth.

[b]BMI = body mass index.

[c]Mean (Standard Deviation).

[d]SSB = Sugar–Sweetened Beverage.

[e]Median [Inter–Quartile Range]

Table 5.3 Multivariate linear regression analyses of the association between SSB[a] intake and metabolic syndrome components in all children of the QUALITY[b] study

Dependent Variable	All subjects (n = 548)		
	β[c] for SSB (100 mL)	***P***	***P*** **(energy adjusted)**
Triglycerides[d] (mmol/L)	0.012	0.273	0.399
HDL–C[d,e] (mmol/L)	0.005	0.521	0.449
HOMA–IR[d,f]	0.024	0.181	0.217
SBP[g,h] (mm Hg)	0.578	0.008	0.004
Waist Circumference[i] (cm)	0.632	0.069	0.066
Fat Mass Index[i] (kg/m^2)	0.189	0.057	0.043
Body Mass Index (kg/m^2)	0.281	0.025	0.019

[a]SSB = Sugar–Sweetened Beverage.

[b]QUALITY = QUébec Adipose and Lifestyle InvesTigation in Youth.

[c]β = regression coefficient.

[d]Models include age, sex, fat mass index and physical activity (counts/minute).

[e]HDL–C = high–density lipoprotein cholesterol.

[f]HOMA–IR = homeostatic model of insulin resistance.

[g]SBP = systolic blood pressure.

[h]Regression for SBP includes all variables from footnote d, plus height.

[i]Fat Mass Index is not controlled for in the regression model of waist circumference, BMI or FMI.

Table 5.4 Multivariate linear regression analyses of the association between SSB[a] intake and metabolic syndrome components in children of the QUALITY[b] study stratified by 85th BMI[c] percentile

Dependent Variable	< 85th BMI percentile (n = 318)			>85th BMI percentile (n = 225)		
	β[d] for SSB (100 mL)	***P***	***P (energy adjusted)***	**β[d] for SSB (100 mL)**	***P***	***P (energy adjusted)***
Triglycerides[e] (mmol/L)	0.012	0.240	0.258	0.014	0.544	0.764
HDL–C[e,f] (mmol/L)	0.009	0.370	0.366	–0.003	0.784	0.986
HOMA–IR[e,g]	–0.027	0.070	0.078	0.097	0.009	0.015
SBP[h,i] (mm Hg)	0.183	0.534	0.330	1.109	0.001	0.001

[a]SSB = Sugar–Sweetened Beverage.

[b]QUALITY = QUébec Adipose and Lifestyle InvesTigation in Youth.

[c]BMI = body mass index.

[d]β = regression coefficient.

[e]Models include age, sex, fat mass index and physical activity (counts/minute).

[f]HDL–C = high–density lipoprotein cholesterol.

[g]HOMA–IR = homeostatic model of insulin resistance.

[h]SBP = systolic blood pressure.

[i]Regression for SBP includes all variables from footnote e, plus height, but age (non–significant) was not controlled.

Table 5.5 Multivariate linear regression analyses of the association between SSB[a] intake and metabolic syndrome components in children of the QUALITY[b] study stratified by glucose tolerance status

Dependent Variable	**Normal Glucose Tolerance (n = 493)**			**Impaired Glucose Tolerance (n = 46)**		
	β[d] for SSB (100 mL)	***P***	***P (energy adjusted)***	**β[d] for SSB (100 mL)**	***P***	***P (energy adjusted)***
Triglycerides[d] (mmol/L)	0.008	0.468	0.614	0.074	0.079	0.078
HDL–C[d,e] (mmol/L)	0.008	0.284	0.240	–0.006	0.722	0.650
SBP[f,g] (mm Hg)	0.493	0.033	0.019	1.443	0.048	0.043
Waist Circumference[d,h] (cm)	0.099	0.785	0.721	4.043	<0.001	0.002
Fat Mass Index (kg/m^2)	0.038	0.713	0.598	1.122	<0.001	0.001

[a]SSB = Sugar–Sweetened Beverage.

[b]QUALITY = QUébec Adipose and Lifestyle InvesTigation in Youth.

[c]β = regression coefficient.

[d]Models include age, sex, fat mass index and physical activity (counts/minute).

[e]HDL–C = high–density lipoprotein cholesterol.

[f]SBP = systolic blood pressure.

[g]Regression for SBP includes all variables from footnote d, plus height, but age (non–significant) was not controlled given the limit of variables with this small subset.

[h]Fat Mass Index is not controlled for in the regression model of waist circumference.

BRIDGE 3

Chapter 4 reports a cross–sectional association between consumption of added sugars from liquid, but not solid sources and several adiposity indicators. Chapter 5 reports that such association between SSB consumption and adiposity and other MetS components is more evident among overweight/obese children or children with IGT. Although some evidence from interventional trials in adults in Chapter 2 suggests that added sugars from liquid and solid sources have different effects on body weight, very little longitudinal evidence has been reported in youth referring to the association between consumption of added sugars (solid vs. liquid) and weight gain. In addition, although a number of cross–sectional studies and two short–term (12 – 16 weeks) behavioral intervention trials in youth have indicated a positive association between added sugar consumption and risk of prediabetes, no cohort study in youth yet examined such association over time.

The QUALITY cohort has robust measures of three 24–hour recalls at baseline, as well as measures of adiposity indicators (i.e., total fat mass by DXA), glucose-insulin homeostasis (fasting glucose and OGTT), physical activity (by 7–day accelerometer) and pubertal status (Tanner stage) at both baseline and 2–year follow–up investigation. All these provide an excellent dataset to test the hypotheses in Chapter 6.

CHAPTER 6. MANUSCRIPT 3

Consumption of added sugars from liquid, but not solid sources predicts impaired glucose homeostasis and insulin resistance among youth at risk of obesity: QUALITY cohort

(This manuscript is pending revision by *J Nutr*)

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6.1 Abstract

OBJECTIVE — To examine the longitudinal associations between added sugar consumption (solid and liquid sources) and changes in adiposity, glucose homeostasis and insulin sensitivity (IS) among youth.

RESEARCH DESIGN AND METHODS — Caucasian children (8–10 y) with at least one obese biological parent were recruited in the QUALITY cohort (n = 630) and followed–up 2 years later (n = 564). Added sugars were assessed by three 24–hour dietary recalls at baseline. Adiposity was measured by fat mass (dual–energy X–ray absorptiometry), body mass index and waist circumference; glucose homeostasis by fasting glucose and oral glucose tolerance tests; IS by fasting insulin, homeostasis model assessment of insulin resistance (HOMA–IR) and Matsuda IS index (Matsuda–ISI). Two–year changes were examined in multivariate linear regression models, adjusting for baseline level, age, sex, Tanner stage, energy intake, fat mass index and physical activity (7–day accelerometer).

RESULTS— Added sugar intake from either liquid or solid sources was not related to changes in adiposity measures. However, a higher consumption (10 g) of added sugars from liquid sources was associated with 0.04 mmol/L higher fasting glucose, 2.1 pmol/L higher fasting insulin, 0.1 unit higher HOMA–IR and 0.3 unit lower Matsuda–ISI ($P < 0.01$) in all participants over two years. No associations were observed with consumption of added sugars from solid sources. Overweight/obese children at baseline had greater increases in adiposity indicators, fasting insulin and HOMA–IR and decreases in Matsuda–ISI over two years than children with BMI below 85th percentile.

CONCLUSIONS: Consumption of added sugars from liquid or solid sources was not associated with changes in adiposity, but liquid added sugars were a risk factor for the development of impaired glucose homeostasis and insulin resistance over two years among youth at risk of obesity.

6.2 Introduction

The prevalence of hyperglycaemia and diabetes is rising globally[1], contributing to a significant increase in morbidity and mortality[2]. Impaired fasting glucose (IFG) and impaired glucose tolerance (IGT) represent intermediate prediabetic conditions in the transition between normal glucose homeostasis and diabetes[3]. The rapid progression from normal glucose homeostasis to the development of prediabetes in children and adolescents underscores the need for prevention[4]. Obesity has been regarded as one of the most important risk factors for developing insulin resistance[5]. In addition, although the diagnosis of type 2 diabetes mellitus (T2DM) is rare among young children, youth are more vulnerable to the development of T2DM at puberty[6]. An analysis of 4,902 adolescents aged 12 to 19 in the U.S. National Health and Nutrition Examination Survey (NHANES, 1999–2002) indicated that the prevalence of insulin resistance was 3%, 15% and 52% in normal–weight, overweight and obese adolescents, respectively[7]. A recent Canadian surveillance study found that 95% of children newly diagnosed with T2DM were obese[6].

Diet worldwide has been sweetening in recent decades, with dramatic increases in the consumption of sweeteners[8]. Although recent data from the United States indicate decreases in the consumption of added sugars, the average intake remains high[9]. Youth are the highest consumers of added sugars, with children aged 9 to 13 years consuming as much as 419 calories per day of added sugars[10]. Added sugars are defined as caloric sweeteners added to foods and beverages during processing or preparation, including sugars and syrups added at the table[11]. Sugar–sweetened beverages (SSB) are the largest source of added sugars in the American diet[12]. Other important sources of added sugar are all from solid food sources, including grain–based desserts, dairy desserts, candies and ready–to–eat cereals[10]. Similarly, in Canada, SSB are also ranked as the top liquid source of total sugars in adolescents, but almost 60% of the average daily total sugar intake in children and adolescents comes from solid sources[13].

A systematic review indicates longitudinal associations between higher intake of added sugars and weight gain in both youth and adults[14]. Evidence from cross–sectional studies in youth and intervention trials in adults suggest that higher levels of added sugar consumption, primarily in the form of SSB, is linked to impaired glucose homeostasis and insulin resistance[15–18], although not all studies support this finding[19–21]. A recent cross–sectional analysis of 2,157 U.S. adolescents in NHANES (1999–2004) indicated that higher consumption of added sugars is not associated with waist circumference (WC) or body mass index (BMI), but is positively associated with a higher homeostasis model assessment of insulin resistance (HOMA–IR) in overweight/obese individuals[16]. In a prospective randomized controlled crossover trial, 29 healthy, normal–weight men (aged 20 to 50 years) were given 600 mL SSB containing different amounts of glucose and fructose (40–80 g/d). The control group was advised to consume low amounts of fructose. After 6 three–week interventions, fasting glucose increased significantly in all experimental participants[18]. However, these above findings were not evident in all studies. To date, there are no cohort studies in children or adolescents examining longitudinal associations between consumption of added sugars and glucose homeostasis and insulin resistance.

In addition, the sources of added sugars (solid vs. liquid) may lead to different influences on adiposity and glucose homeostasis. Two randomized controlled trials[22, 23] in adults suggest that only added sugars from liquid sources promote positive energy balance and a reduction in liquid added sugar intake had a stronger effect than did a reduction in solid added sugar intake on weight loss. To date, however, only one longitudinal study in youth examined such potential differences[24]. A sample of 2,139 Finnish children and adolescents (3 to 18 years at baseline) were followed–up for a period of 21 years and the results indicated that increased consumption of added sugars from liquid sources (SSB) from childhood and adolescence to adulthood is associated with overweight in women (not in men), but no such association was found with consumption of added sugars from solid source (sweets). Considering the large proportion of added sugars consumed

among youth come from solid sources, the American Heart Association (AHA) recently called for further evidence on the effects of consuming dietary sugar from solid versus liquid sources on cardiovascular health[11]. This current study was designed to determine if added sugar consumption is associated with the changes in adiposity, impaired glucose homeostasis or insulin sensitivity in a sample of Canadian youth at risk of obesity, and to assess whether associations differed according to the sources of added sugars (solid vs. liquid).

6.3 Methods

The study is a secondary analysis of data from the QUébec Adipose and Lifestyle InvesTigation in Youth (QUALITY) study, an ongoing prospective cohort investigation. The sample included 630 children aged 8 to 10 years at baseline (2005–2008), of whom 564 children finished the investigation at the 2–year follow–up (47 refused and 19 were lost to follow–up). All analyses in this study were restricted to these 564 children. Due to missing data, the final sample size for regression analyses was 558 (for total fat mass), 564 (for BMI and waist circumference), 548 (for fasting glucose, fasting insulin and HOMA–IR) and 524 (for Matsuda–ISI) respectively. Methods for this study have been previously described in detail[25]. All children were at risk of obesity since the inclusion criteria required that at least one biological parent had a BMI $\geq$ 30 kg/m^2 or central obesity (WC > 88 cm for women and > 102 cm for men). The selection criteria for children also included no diagnosis of diabetes, not following a very restricted diet (< 600 kcal/d), no regular medications and no serious psychological ailments. Anthropometry and physical activity were assessed, and blood samples were collected both at baseline and at the 2–year follow–up. Interviewer–administered questionnaires, and biological and physiological measurements among children were carried out during a full–day visit at the Unité de recherche clinique du Centre Hospitalier Universitaire Sainte–Justine in Montreal or Hospital Laval in Québec City. This project was approved by the ethics review boards at Centre Hospitalier Universitaire Sainte–Justine and Laval University.

Written informed assent and consent was obtained from children and their parents, respectively.

6.3.1 Dietary assessment

Dietary assessment was undertaken at baseline in three 24–hour dietary recalls on non–consecutive days of the week, including one weekend day. All dietary records were completed by a registered dietitian 8–12 weeks after the clinic visit. In order to minimize the response burden to families, recalls were conducted by telephone interview. During the clinic visit, each participant received a disposable kit of food portion size models (i.e., a graduated cup, bowl and other portion size models). Both children and their parents were given a short training session on the use of the models. Interviews were conducted with the child, and parents helped with food descriptions and cooking details when necessary. All dietary data were entered into the CANDAT Nutrient Analysis Software (Godin London Incorporated, London, ON, Canada), which provides a nutrient analysis based on the Canadian Nutrition Files (CNF) 2007b and 2010 (2010 version was used for estimating added sugars only). It allows for the creation of food groups, in this case liquid and solid forms of added sugar. In all, 551 of 564 participants completed three 24–hour dietary recalls.

As the CNF provides data on total sugars only, the U.S. Department of Agriculture (USDA) Database for the Added Sugars Content of Selected Foods was used for estimating added sugars[26]. If the USDA and CNF values for total sugars were the same, USDA added sugar values were recorded without modification. If the exact or similar item was in the USDA database, but the total sugars values differed from the CNF, the total sugar values from the CNF was retained and the added sugar values from the USDA database were modified using the formula: added sugars = [added sugars (USDA database) × total sugars (CNF)]/total sugars (USDA database). For foods with missing total sugars values, Nutrition Facts labels found on the manufacturer's websites were used. In the case

of items which did not have Nutrition Facts labels, the total sugar values were taken from the most similar food item.

Added sugars were categorized into liquid and solid food sources. Liquid sources included SSB and flavoured milk (FM). A food group was created for SSB in CANDAT, which included soft drinks, fruit drinks, sports drinks and sweetened tea (but not diet drinks or 100% fruit juice). The FM group was created to include ready–to–drink chocolate or other–flavored milks and homemade FM (plain milk to which chocolate flavor powder or syrup was added). Added sugars from solid sources were calculated as total added sugars minus added sugars from liquid sources.

6.3.2 Anthropometric measurements

At each clinic visit, anthropometric characteristics were measured according to standardized protocols[27], including height (stadiometer), weight (electronic scale) and WC (standard measurement tape). Age–and–sex specific BMI percentiles for children were computed using the Center for Disease Control and Prevention (CDC) growth charts[28]. Fat mass was determined with dual energy X–ray absorptiometry (DXA, Prodigy Bone Densitometer System, DF+14664, GE Lunar Corporation, Madison, WI, USA)[29], which was converted into a fat mass index (FMI) by dividing total fat mass (kg) by height squared (m^2)[30]. All baseline participants were subcategorized into two groups: overweight/obese (BMI $\geq 85^{th}$ percentile) and normal–weight (BMI $< 85^{th}$ percentile). Pubertal stage was scored by trained nurses according to Tanner[31, 32] as a means of controlling for differences among children in maturational development not captured in reference growth curves for BMI[33].

6.3.3 Oral glucose tolerance test

At each clinic visit, blood samples were obtained from each child by venipuncture, after an overnight fast. A 120–min oral glucose tolerance test (OGTT) was performed and blood was collected at 30, 60, 90, and 120 min after

an oral glucose dose of 1.75 g/kg body weight (up to a maximum of 75 g). Blood samples were centrifuged, aliquotted and stored at –80℃ until analysed for fasting glucose. All biochemical analyses were conducted at the Department of Clinical Biochemistry of the Centre Hospitalier Universitaire Sainte–Justine. HOMA–IR was calculated from fasting glucose and insulin; higher levels indicate greater insulin resistance[34]. HOMA–IR has been validated as a simple and practical method to measure insulin resistance in children and adolescents[35]. Insulin sensitivity (IS) was assessed by Matsuda–IS index (Matsuda–ISI), which was calculated as 10,000/square root [(fasting glucose × fasting insulin) × (mean OGTT glucose × mean OGTT insulin)][36]; lower values indicate decreased IS. The Matsuda–ISI has been validated against the current gold standard method as one of the best OGTT–based indices for estimating IS in children[37].

6.3.4 Physical activity measurement

Participants' physical activity was measured using a uniaxial activity monitor (Actigraph LS 7164 activity monitor, Actigraph LLC, Pensacola, FL, USA) for 7 days in the week following the clinic visit. To keep consistent with current procedures used by the Canadian Health Measures Survey[39], a minimum of 4 days was required and days were excluded when the accelerometer was worn for less than10 hours. Ninety–seven percent of children had more than 4 days of accelerometer data with a mean of 13.4 hours daily in the unit of counts per minute[38], which has been shown to ensure adequate reliability[40]. The Actigraph accelerometers have been validated against activity based energy expenditure assessed by doubly–labeled water in 9 year old children ($r = 0.58$)[41] .

6.3.5 Statistical analysis

Added sugar intake, covariate measures, indicators of adiposity, glucose homeostasis and insulin resistance were described in all children who participated in the investigations at both baseline and follow–up and in the two weight–based subgroups (overweight/obese vs. normal–weight subjects) using proportions and means (standard deviation). Independent t–tests were used to compare 2–year

changes in outcome variables (fat mass, BMI, WC, fasting glucose, fasting insulin, HOMA–IR and Matsuda–ISI) between overweight/obese and normal–weight individuals. In the multivariate linear regression models, 2–year changes in outcome variables were separately examined in all participants and in the two subgroups, adjusting for the baseline value of the outcome variable, as well as age, sex, Tanner stage, energy intake, FMI and physical activity. Separate strata by weight group were used because interaction terms (added sugars × overweight status at baseline, for both solid and liquid added sugars) were statistically significant for several outcome variables (fasting glucose and HOMA–IR) in the regression models. The β–coefficients were used to describe changes in the outcome variables associated with 10 g increase in added sugar intake. All statistical analyses were conducted using STATA 11.0 (StataCorp LP, College Station, TX, USA). The significance level was set at 5% (two–tailed).

6.4 Results

Added sugar intake level and covariates controlled for in regression models of the QUALITY study participants at baseline are described in Table 6.1. The average consumption of added sugars from solid and liquid sources was 40.4 g and 11.4 g respectively in all participants. The average age for all participants was 9.6 years at baseline, with 55.5% as boys, and 41.1% were classified as overweight/obese. Daily average energy intake was 1,702 kcal for all participants, with no significant difference between the two subgroups. Overweight/obese children consumed less solid added sugars, had a higher FMI and a higher percentage above Tanner stage 1 and were less physically active than normal–weight children.

Over 2 years, an average increase in weight (+11.3 kg), fat mass (+4.3 kg), BMI (+1.7 kg/m^2) and WC (+5.3 cm) was observed in all participants, with significantly greater increases among overweight/obese children compared with normal–weight children (Table 6.2).

Metabolic indicators of glucose and insulin resistance are presented in Table 6.3. The levels of fasting glucose (+ 0.1 mmol/L), fasting insulin (+13.8 pmol/L) and HOMA–IR (+0.4 unit) all increased over time, while Matsuda–ISI (–2.5 unit) decreased on average among all participants. Overweight/obese children had significantly greater increases in both fasting insulin and HOMA–IR. A significantly greater decrease of Matsuda–ISI was detected in normal–weight children compared with overweight/obese children; this may be because more overweight/obese children had entered puberty at baseline compared with normal–weight children, but these differences were not as present at the 2–year follow–up.

The results of the multivariate linear regression analyses of the longitudinal associations between intake of added sugars (solid vs. liquid) and 2–year changes in the outcome variables are displayed in Table 6.4. There were no statistically significant associations between consumption of added sugar (solid or liquid sources) and 2–year changes in fat mass, BMI or WC. In all participants combined, each additional 10–g added sugars from liquid sources was associated with 0.04 mmol/L higher fasting glucose ($P < 0.01$), 2.3 pmol/L higher fasting insulin ($P < 0.01$), 0.1 unit higher HOMA–IR ($P < 0.01$) and 0.4 unit lower Matsuda–ISI ($P < 0.01$) over 2–year follow–up. In stratified analyses based on baseline weight category, stronger associations between added sugars from liquid sources and HOMA–IR were observed in overweight/obese children. No associations were detected between consumption of added sugars from solid sources and 2–year changes in the indicators of glucose homeostasis or insulin sensitivity.

6.5 Discussion

Although many studies have examined the associations between consumption of added sugars in liquid form of SSB and weight gain in both youth and adults, no study in youth has previously provided evidence of longitudinal associations between added sugar consumption and glucose homeostasis and insulin

resistance. Our study found that consumption of added sugars from liquid, but not solid sources predicted a higher risk of impaired glucose homeostasis (i.e., increased fasting glucose) and insulin resistance (i.e., increased fasting insulin, HOMA–IR and decreased Matsuda–ISI) over a 2–year period in childhood. There was no association between consumption of added sugars from either solid or liquid sources and changes in adiposity.

Research on the association between added sugar consumption and adiposity is still inconclusive. Although a number of studies in several recent review articles have suggested a positive link between intake of added sugars (mostly from SSB) and weight gain in youth[42, 43], negative findings were also reported. A longitudinal study of 2,139 Finnish youth (3 to 18 years at baseline) reports no association between consumption of added sugars from solid source (sweets) at youth and being overweight in adulthood over 21 years[24]. Another longitudinal study of 1,203 British children found no evidence of an association between SSB consumption at age 5 or 7 y and total fat mass at 9 y[44]. Our findings are in agreement with the above two cohort studies, no associations with adiposity measures were observed with consumption of added sugars. The relatively low consumption levels of added sugars from SSB in our study may mask the actual association with weight gain. Some evidence shows the consumption of flavoured milk (the other liquid source of added sugars) is not associated with adiposity indicators[45, 46]. Very few studies[21, 24] have examined the association between consumption of solid added sugars and adiposity in youth and these report either no or negative association. When examining added sugars as a whole, results might vary depending on the proportion of solid versus liquid source. In addition, consumption of added sugars, particularly from SSB, may be a marker of an overall unhealthy lifestyle, rather than a specific risk factor for weight gain[44]. Further longitudinal evidence on consumption of added sugar from both sources and weight gain in youth is warranted.

Several cross–sectional studies and randomized controlled trials in youth have reported associations between dietary sugar intake and the risk of prediabetes. Davis et al. examined 120 overweight Latino youth (10–17 y) and reported that higher dietary sugar intake was associated cross–sectionally with lower IS and lower measures of insulin secretion[47]. Another recent cross–sectional analysis of 546 European adolescents indicated that frequent consumption of SSB (≥ 5–6 times/week) was related to increased HOMA–IR[15]. A behavioral intervention trial in 54 overweight Latino adolescents randomly assigned individuals in the control and intervention group. After 16 weeks, it was found that individuals in the intervention group who reduced added sugar intake by the equivalent of 355 mL of soda per day showed significant improvement in insulin secretion[48]. In addition, most current studies[42], including our previous cross–sectional findings with QUALITY participants[17], only provide evidence for intake of SSB or added sugars as a whole. We firstly examined added sugar intake from liquid and solid sources and found that liquid, but not solid added sugar predicted an increased level of fasting glucose, fasting insulin, HOMA–IR and a decreased Matsuda–ISI over 2 years, independent of adiposity. In addition, the increase in HOMA–IR associated with liquid added sugar consumption was more evident in children who were overweight/obese at baseline.

To date, studies comparing the impact of added sugars from liquid versus solid foods have been conducted only in adults. In an early cross–over design, 7 males and 8 females were given sugar loads (450 kcal/d) as a liquid (soda) or solid (jelly beans) during two 4–week periods separated by a 4–week washout. The authors reported that only liquid sugars promoted positive energy balance and increased body weight (BMI)[22]. A prospective study of 810 adults participating in an 18–month randomized controlled behavioural intervention trial found that a reduction in liquid energy intake (SSB) had a stronger effect on weight loss than did a reduction in calories from all solid foods[23]. A recent cross–sectional study of 15,023 adults from NHANES (1999–2004) suggested that consumption of added sugars from solid sources (candy) was not associated with body weight or other

risk factors for cardiovascular disease[19]. One possible mechanism is that dietary compensation is weaker for sugar intake from beverages than for solid food forms of comparable nutrient content[49].

The QUALITY cohort has several strengths including robust measures of adiposity indicators (fat mass, by DXA), glucose homeostasis and insulin sensitivity (by OGTT) and physical activity (by accelerometry) at both baseline and follow–up in a large number of children[50]. In addition, the detailed three 24–hour dietary recalls at baseline enabled us to estimate added sugar values from both solid and liquid food sources. Underreporting is prevalent among self–reports of dietary surveys among both youth and adult populations[51]. Specific food items particularly "unhealthy" foods rich in fat and/or added sugars (such as SSB, sweets and fast foods etc.) are more frequently underestimated during dietary recalls[52]. It is also found that underreporting increases with BMI, but underestimation of energy intake is not confined to overweight subjects[53]. Thus, the associations demonstrated in this study may be even stronger if the dietary intake were more accurately noted. In addition, despite the relatively low consumption levels of added sugars from SSB in this study, clear associations with glycemic indicators were present in our data. Although the generalizability of the findings may be restricted to youth with at least one obese parent, this group comprises a substantial number of children in the general population, given the elevated prevalence rates of obesity in adults. Recruitment from schools rather than clinics also helps to enhance the generalizability.

The preference for sweet–tasting foods and beverages likely relates to high consumption of sugars, especially among children and adolescents[54]. To date, no specific recommendations have been made on an upper cut–off level for the quantity of added sugars for healthy children. The average daily intake of added sugars in QUALITY participants was 204 kcal, higher than the recommendation proposed by AHA to reduce added sugar intake to no more than 100 kcal/d and 150 kcal/d for most American women and men, respectively[11]. The availability of

sugar–sweetened foods and beverages at home, in schools and in neighbourhoods (such as in corner stores etc.) all influence youths' food choices. The America on the Move Family Study demonstrates the effectiveness of preventing excess weight gain through a "small–changes" approach, such as eliminating 100 kcal per day from usual diets by replacing dietary sugars with a noncaloric sweetener[55]. School–based intervention programs such as the School Nutrition Policy Initiative[56] and the Health Corner Store Initiative[57] provide evidence that changing the dietary environment (i.e., in the cafeteria, vending machines etc.) in schools and corner stores can effectively prevent weight gain in youth.

6.6 Conclusion

This study detected longitudinal associations between added sugar intake in liquid form and a higher risk of impaired glucose homeostasis and insulin sensitivity. Increased focus on reducing the consumption of added sugars, especially from liquid sources may be a useful strategy to prevent the development of prediabetes in youth.

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Table 6.1 Baseline data on QUALITY[a] study participants stratified by weight status

	All (n = 564)[b]	**Overweight/obese (n = 232)**	**Normal–weight (n = 332)**
Age (years)	9.6 (0.9)[c]	9.7 (0.9)	9.5 (1.0)
Boys (%)	55.5	56.0	55.1
Tanner stage > 1 (%)	19.7	26.2**	16.0
Energy intake (kcal)	1702 (392)	1705 (407)	1700 (383)
Fat mass index (kg/m^2)	5.4 (3.3)	8.5 (2.9)***	3.2 (1.3)
Accelerometer (counts/min)	587 (184)	554 (162)**	609 (195)
Added sugars (solid sources, g)	40.4 (22.2)	37.7 (20.4)*	42.2 (23.2)
Added sugars (liquid sources, g)	11.4 (12.5)	12.1 (12.9)	10.8 (12.2)

[a] QUALITY = QUébec Adiposity and Lifestyle InvesTigation in Youth;

[b] Due to missing data for some participants, the actual number is 551 (for added sugars and energy intake), 550 (for Tanner stage), 558 (for fat mass index) and 475 (for accelerometer).

[c] Mean (Standard Deviation);

***$P < 0.001$, **$P < 0.01$, *$P < 0.05$, compared between overweight/obese (BMI ≥ 85th percentile at baseline) and normal–weight (BMI < 85th percentile at baseline) participants.

Table 6.2 Adiposity indicators of QUALITY[a] study participants at baseline, follow–up and 2–year changes stratified by weight status

Characteristics	Baseline	Follow–up	2–year changes
Weight (kg)			
All (n = 564)	37.8 (11.1)	49.1 (14.8)	11.3 (5.5)
Overweight/obese (n = 232)	47.1 (10.8)	62.1 (13.6)	14.2 (6.1)***
Normal–weight (n = 332)	31.3 (4.9)	41.0 (7.3)	9.2 (3.9)
Total fat mass (kg)			
All (n = 558)	10.7 (7.4)	14.9 (9.6)	4.3 (3.8)
Overweight/obese (n = 231)	17.3 (6.9)	24.1 (8.8)	6.1 (4.5)***
Normal–weight (n = 327)	6.1 (2.7)	9.2 (3.8)	3.0 (2.5)
BMI (kg/m^2)			
All (n = 564)	19.4 (4.2)	21.1 (4.9)	1.7 (1.7)
Overweight/obese (n = 232)	23.3 (3.7)	25.9 (4.2)	2.2 (2.2)***
Normal–weight (n = 332)	16.6 (1.4)	18.1 (1.8)	1.4 (1.2)
Waist circumference (cm)			
All (n = 564)	67.1 (11.8)	72.4 (13.3)	5.3 (5.2)
Overweight/obese (n = 232)	77.9 (10.6)	85.1 (11.4)	6.3 (6.7)***
Normal–weight (n = 332)	59.5 (4.5)	43.0 (3.0)	4.6 (3.6)

[a] QUALITY = QUébec Adiposity and Lifestyle InvesTigation in Youth;

[b] Mean (Standard Deviation);

$^{***}P < 0.001$, $^{**}P < 0.01$, $^{*}P < 0.05$, compared between overweight/obese (BMI ≥ 85th percentile at baseline) and normal–weight (BMI < 85th percentile at baseline) participants.

Table 6.3 Indicators of glucose homeostasis and insulin sensitivity of QUALITY[a] study participants at baseline, follow–up and 2–year changes stratified by weight status

Characteristics	Baseline	Follow–up	2–year changes
Fasting Glucose (mmol/L)			
All (n = 548)	4.9 (0.4)	5.1 (0.4)	0.10 (0.39)
Overweight/obese (n = 224)	5.0 (0.4)	5.1 (0.4)	0.12 (0.36)
Normal–weight (n = 324)	4.9 (0.3)	5.0 (0.4)	0.08 (0.43)
Fasting Insulin (pmol/L)			
All (n = 548)	32.2 (21.0)	46.3 (30.6)	13.8 (23.5)
Overweight/obese (n = 224)	44.9 (25.1)	66.1 (35.8)	19.1 (30.4)***
Normal–weight (n = 324)	23.5 (11.1)	33.4 (16.7)	10.0 (15.8)
HOMA–IR			
All (n = 548)	1.0 (0.7)	1.5 (1.1)	0.4 (0.8)
Overweight/obese (n = 224)	1.4 (0.8)	2.1 (1.3)	0.6 (0.1)***
Normal–weight (n = 324)	0.7 (0.4)	1.1 (0.6)	0.3 (0.6)
Matsuda–ISI			
All (n = 524)	10.3 (5.6)	7.6 (4.8)	–2.5 (4.5)
Overweight/obese (n = 209)	6.8 (3.3)	5.4 (3.3)	–1.3 (3.1)***
Normal–weight (n = 315)	12.6 (5.7)	9.2 (5.2)	–3.2 (5.1)

[a] QUALITY = QUébec Adiposity and Lifestyle InvesTigation in Youth;

[b] Mean (Standard Deviation);

$^{***}P < 0.001$, $^{**}P < 0.01$, $^{*}P < 0.05$, compared between overweight/obese (BMI $\geq 85^{th}$ percentile at baseline) and normal–weight (BMI $< 85^{th}$ percentile at baseline) participants.

Table 6.4 Multivariate linear regression analyses of associations between baseline intake of added sugars and 2–year changes in the indicators of adiposity and glucose homeostasis and insulin sensitivity among QUALITY[a] study participants stratified by weight status

	β for solid added sugars (10 g)	95% CI	β for liquid added sugars (10 g)	95% CI
Adiposity				
Δ Total fat mass (kg)				
All (n = 472)	–0.039	[–0.207, 0.130]	–0.041	[–0.288, 0.205]
Overweight/obese (n = 197)	–0.093	[–0.480, 0.293]	–0.296	[–0.792, 0.200]
Normal–weight (n = 289)	–0.003	[–0.051, 0.145]	0.173	[–0.058, 0.405]
Δ BMI (kg/m^2)				
All (n = 472)	–0.014	[–0.098, 0.070]	–0.005	[–0.128, 0.117]
Overweight/obese (n = 197)	–0.037	[–0.228, 0.155]	–0.122	[–0.368, 0.125]
Normal–weight (n = 289)	0.003	[–0.071, 0.076]	0.102	[–0.012, 0.217]
Δ WC (cm)				
All (n = 472)	–0.076	[–0.330, 0.179]	0.159	[–0.214, 0.531]
Overweight/obese (n = 197)	–0.127	[–0.695, 0.440]	0.144	[–0.586, 0.874]
Normal–weight (n = 289)	0.007	[–0.219, 0.232]	0.182	[–0.170, 0.535]
Glucose homeostasis				
Δ Fasting Glucose (mmol/L)				
All (n = 457)	0.001	[–0.016, 0.018]	0.039	[0.015, 0.063]**
Overweight/obese (n = 186)	–0.007	[–0.039, 0.026]	0.039	[0.001, 0.079]*
Normal–weight (n = 271)	0.005	[–0.015, 0.024]	0.039	[0.010, 0.070]*

[a] QUALITY = QUébec Adiposity and Lifestyle InvesTigation in Youth;

Covariates include baseline level of the outcome variable, age, sex, Tanner stage, energy intake, FMI and physical activity.

$^{**}P < 0.01$, $^{*}P < 0.05$ for β–coefficients in the regression models.

Table 6.4 Multivariate linear regression analyses of associations between baseline intake of added sugars and 2–year changes in the indicators of adiposity and glucose homeostasis and insulin sensitivity among QUALITY[a] study participants stratified by weight status (cont'd)

	β for solid added sugars (10 g)	95% CI	β for liquid added sugars (10 g)	95% CI
Glucose homeostasis				
Δ Fasting Insulin (pmol/L)				
All (n = 457)	0.196	[–0.904, 1.296]	2.261	[0.676, 3.845]**
Overweight/obese (n = 186)	1.442	[–1.068, 3.953]	2.910	[–0.272, 6.091]
Normal–weight (n = 271)	0.245	[–0.637, 1.127]	1.238	[–0.147, 2.674]
Δ HOMA–IR				
All (n = 457)	0.007	[–0.033, 0.047]	0.091	[0.034, 0.149]**
Overweight/obese (n = 186)	0.047	[–0.046, 0.140]	0.121	[0.013, 0.247]*
Normal–weight (n = 271)	0.011	[–0.021, 0.042]	0.046	[-0.003, 0.096]
Δ Matsuda–ISI				
All (n = 419)	–0.036	[–0.227, 0.156]	–0.356	[–0.628, –0.084]**
Overweight/obese (n = 165)	0.006	[–0.263, 0.275]	–0.258	[–0.581, 0.065]
Normal–weight (n = 254)	–0.070	[–0.338, 0.198]	–0.331	[–0.749, 0.087]

[a] QUALITY = QUébec Adiposity and Lifestyle InvesTigation in Youth;

Covariates include baseline level of the outcome variable, age, sex, Tanner stage, energy intake, FMI and physical activity.

$^{**}P < 0.01$, $^{*}P < 0.05$ for β–coefficients in the regression models.

CHAPTER 7. PUBLIC HEALTH MESSAGES

The scientific evidence base (Chapter 2) is becoming increasingly robust and demonstrates that added sugars, especially those from sugar–sweetened beverages (SSB), increase the risk of adiposity and other metabolic syndrome (MetS) components. The findings in this thesis (Chapters 4–6) provide further evidence that consumption of added sugars from both solid and liquid sources is associated with a lower overall diet quality; the association between higher levels of SSB intake and MetS components are more evident among overweight/obese and glucose–intolerant children; and consumption of liquid added sugars is clearly associated with development of impaired glucose homeostasis and insulin resistance over 2 years among a sample of Canadian children at risk of obesity.

It is estimated that 75% to 90% of the CVD epidemic is related to obesity, dyslipidemia, hypertension, diabetes mellitus, tobacco use, and physical inactivity; the principal causes of these risk factors are behavioral, including poor nutrition[1]. Balanced nutrition, a physically active lifestyle, moderate wine consumption and absence of tobacco use contribute to a lower prevalence risk and assist in either delaying or preventing the onset of CVD[2]. The relation between added sugar consumption (especially from SSB), obesity and related metabolic health outcomes has increasingly attracted scientific and public interest[3]. Limiting added sugar consumption among children and adolescents, especially from its liquid source of SSB, is important considering a rising prevalence of obesity and other MetS components in this population. It could be an effective strategy to prevent the early onset of type 2 diabetes mellitus (T2DM) and CVD by improving weight status, lipid profiles, insulin sensitivity and reducing blood pressure[4]. Public health education undertaken among health care communities, integrated with health policy and environmental change to enhance optimal nutrition and physical activity, are essential to the primary prevention[5].

7.1 Dietary guidelines

Statements from the American Heart Association, the American Academy of Pediatrics, and the U.S. 2010 Dietary Guidelines technical review committee all propose to reduce SSB consumption to prevent obesity and improve metabolic health[6]. But until recently there was no quantifiable recommendation for added sugars[7]. The 2000 Dietary Guidelines for Americans (DGA) advised consumers to choose beverages and foods with *moderate* sugar intake[8] and the 2005 DGA advised Americans to choose prepared food and beverages with *little* added sugars or caloric sweeteners[9]. The Institute of Medicine[10] macronutrient report did not recommend a tolerable upper intake level for total or added sugars, but did suggest a maximal intake level of 25% or less of energy from added sugars for both children and adults. Part of the rationale for this recommendation was concern about low micronutrient intake of persons whose diet exceeded 25% of energy from added sugars. In 2006, the Diet and Lifestyle Recommendations from the AHA Nutrition Committee advised to *minimize* intake of foods and beverages with added sugars[11]. In 2009, the AHA made a first specific recommendation for added sugar intake based on people's energy needs that most American women should limit their daily added sugar intake to *no more than 100 kilocalories* and for most American men, the recommendation is *no more than 150 kilocalories* per day[12]. In 2010, DGA Advisory Committee stated that among several strategies to reduce the incidence and prevalence of overweight and obesity, consumers should *avoid* SSB[13]. To date, no specific recommendation for children and adolescents has been made.

The Nutrition Facts label, which is composed of the amount of kilocalories and 13 core nutrients in a usual serving size, is mandatory on majority of pre–packaged foods in both U.S. and Canada[14, 15]. The total amount of carbohydrate and two specific subsets (sugars and fibre) in a usual serving size of food/beverage are required to be listed on the Nutrition Facts label. Within the core list, the content of sugars includes those naturally in or added to foods[15]. Daily Values (DVs) are designed by the Food and Drug Regulations as "reference standards" for most

nutrients in the Nutrition Facts label. For example, the DV for carbohydrate is 300 grams, of which the estimation is based on a 2000–kilocalorie reference diet, and it indicates that the diet should provide 55% of energy as carbohydrate from a variety of sources. In the Nutrition Facts label, nutrient content is expressed as a percentage of the DV. No percentage of DV was set for sugars considering there is no generally accepted sugar consumption level among healthy populations[15].

Currently, Nutrition Facts label in the U.S. and Canada contains the content information on total sugars per serving, but do not distinguish sugars that are naturally present or added to foods[14, 15]. Therefore, consumers could not easily determine the amount of added sugars in foods and beverages. Technically, there is no method to particularly analyze the added sugar content in the foods, therefore its amounts must be extrapolated or provided by food companies. In 2006, the U.S. Department of Agriculture (USDA) published a *Database for the Added Sugars Content* that dietetics practitioners can use to help educate consumers[16]. In addition, there are several ways to identify added sugars in processed and prepared foods[7]: (i) search the ingredient list for the word *syrup*, such as corn syrup, high–fructose corn syrup, maple syrup etc.; (ii) look for words ending in "ose", such as fructose, glucose, sucrose and dextrose; (iii) compare the unsweetened version of a product (plain, unsweetened yogurt or plain shredded wheat cereal) with the sweetened version (fruit–flavoured yogurt or frosted shredded wheat) to estimate the amount of added sugars by a simple substruction; (iv) if a food contains little or no milk or fruit (fructose in fruit and lactose in milk and dairy products are naturally occurring), the sugar value on the package's Nutrition Facts label will help for the estimation of added sugars in each serving; (v) artificial sweeteners listed on the ingredients (such as aspartame, sucralose, saccharin, cyclamate and etc.) do not belong to added sugars, because they are energy free. Furthermore, several voluntary food labeling systems are already pronounced in market or are being developed, some of which include criteria for limiting excessive use and consumption of added sugars, such as the Smart Choices Program[17], the Overall Nutrient Quality Index[18], the Nutrient Rich Foods

Coalition nutrient density score[19] and the Hannaford's grocery chain Guiding Stars program[20].

7.2 Changes in dietary environments

Although some evidence shows that added sugar consumption decreased in the past decade in the U.S., their mean intake remains high[21]. The preference of sweet–tasting foods and beverages induces high consumption of sugars, especially for children and adolescents[22]. Children's added sugar consumption, especially from SSB, has been a focus of dietary environment research, such as the availability and regulation of competitive foods and beverages at schools[23, 24]. Parents, schools, and the media exert influence in shaping the dietary attitudes and behaviors of youth, from infancy to adolescence[25, 26]. Especially, school nutrition and price policies directed at SSB consumption can play an important role in reducing energy intake and adiposity in youth[25]. In addition, prices (taxes and incentives) have the potential to reduce SSB consumption[27].

For children and adolescents, schools have become a battleground for fighting the obesity epidemic[28, 29]. School nutrition education program is considered useful to improve students' healthy dietary knowledge, but some evidence also indicates that it is not effective in altering eating behaviors without changes in the dietary environment[29]. As of the 2008 to 2009 school year in the U.S., high–energy beverages and beverages not allowed by national guidelines were still widely available in elementary schools from any venue on campus (vending machines, stores, snack bars, and/or à la carte). The percentage of public school students with access to SSB dropped from 17.3% (2006 to 2007 year) to 14.1% (2008 to 2009 year), whereas this percentage from private elementary schools dropped from 40.5% to 38.4%[30] which was still high. In addition, most students with access to competitive venues could purchase sweet products (i.e. candy, baked products), but healthier foods (such as fruits and vegetables) were less widely available[31]. The offering of flavoured milk (FM) in school meals has been debated, with some arguing that milk–related nutrient benefits outweigh the

empty calories from added sugars[32]. FM consumption is significantly higher at school than at home or other locations and is highest among elementary schoolchildren (51%, on a typical school day)[24]. On average, replacing SSB and FM with water (at non–meals) or unflavoured milk (at meals) translates to an estimated daily savings of 205 kilocalories per student. Such improvements in beverage selections are expected with savings of 10% of total daily energy intake and 52.5 g of daily added sugar intake in school children[24]. Food and drinks in vending machines are usually with low nutrient density, but also itself provides revenue to support school lunch programs. Cafeterias are often blamed for serving unhealthy food, but considering the food provided is more constrained by budget or related regulatory issues which is widely external to general public health concerns[33].

On a typical school day, children consume on average 34% of kilocalories at schools, while 56% at home and another 10% at other locations[34]. The food environment at both home and schools is associated with children's overall consumption of SSB[34] and a significantly higher proportion is noticed at home[24]. Parents play an important role in establishing a model of healthy food choices for their children[35]. Parents could act as either positive or negative roles, depending on their own dietary behaviors[36]. Beverage interventions aimed at parents, especially mothers, shows the influence on children's SSB purchasing behaviors and consumption at home and at fast–food restaurants[37].

Media also has a pervasive influence on children's food choices. Children are usually the marketed targets by the food industry. Evidence shows that television hours are significantly related to children's food requests[38]. The most frequently and widely advertised foods include SSB, high–sugar breakfast cereals, frozen dinners, cookies, candy and fast food restaurant products[39]. In addition, watching television during meals is suggested to link with reduced frequency of good food choices but increased frequency of unhealthy food[39, 40]. Quebec and several

European countries now have published rules on restricting food advertisement to children and school–based marketing[33, 41].

The availability of high added sugar foods and beverages at home, school and nearby environment (like corner stores etc.) all influence youths' food choices. The America on the Move Family Study demonstrates the effectiveness of preventing excess weight gain through small–changes of eliminating 100 kcal per day from their typical diet by replacing dietary sugars with a noncaloric sweetener[42]. School–based intervention programs like the HEALTHY[43] and the School Nutrition Policy Initiative[44] as well as beyond school environment program like the Health Corner Store Initiative[45] all provided messages that changing the dietary environment (cafeteria, vending machines etc.) in school and corner stores can be effective in preventing weight gain in youth.

7.3 Challenges and opportunities for government and industry

Governments are now becoming active in the effort to control the escalation of obesity and diet–related comorbidities using potential policy instruments to incentivize consumers to improve their food and beverage consumption patterns and related health outcomes[46, 47]. The further regulation is suggested to include providing more information in food labeling, restricting unhealthy foods supplied to children, and requesting restaurants to provide nutrition information[48, 49]. Several states in the U.S. and some European countries have tried taxation as a way of reducing SSB consumption as well as offsetting the raised health care costs due to excessive intake of these beverages[50].

In addition, numerous regulatory strategies are already undertaken to reduce SSB consumption, despite attempts from the beverage industry to disturb by funding biased analyses and reviews, or by supplying consumers with misleading information[50]. For example, the Beverage Guidance Panel has recommended limiting SSB intake for general population in the U.S.[51]. Not only governments at national and subnational levels, but also some beverage industries have taken

voluntary actions to restrict the availability of SSB in schools[52–54]. As for the regulation of FM, although several recommendations or policies have been announced, no definite agreement has been reached to date. Food and Nutrition Service in the U.S. published Nutrition Standards for School Meals allowing schools to offer FM only if it is fat–free[55]. The dairy industry is also working to reduce the amount of added sugars in FM offered to schools[7]. A study of U.S. public elementary schools which provided low–calorie and standard FM and found that none of the FM sampled in these schools were in full compliance with either the proposed USDA regulation[55], or the Institute of Medicine recommendations[56, 57]. In addition, Recommended Community Strategies published by Center for Disease Control and Prevention (CDC) required licensed child care facilities within the local jurisdiction to ban SSB (including FM)[58], so did Los Angeles Unified School District Board of Education which has voted to remove FM from schools[59].

Many challenges are still existed to incorporating added sugar content to the Nutrition Facts label, but such disclosure is essential in nutrition education to motivate healthier food choices[14]. It will take time for the food environments to change, but parents and dietetics practitioners can continue to help children and adolescents make changes to lower the amount of added sugars in the diets to the current AHA recommendation levels to achieve and maintain healthy body weights, improve diet quality and meet essential nutrient needs, and lower risk for CVD[7].

7.4 References

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CHAPTER 8. OVERALL SUMMARY AND CONCLUSION

This dissertation assessed the relationship between consumption of added sugars, dietary intake and metabolic health in a sample of Canadian school children who were at risk of obesity. We found that higher dietary intake of added sugars, from either solid or liquid food sources, is linked to a lower overall diet quality in children, while SSB further contributes to a lower nutrient dense diet by replacing milk intake. Liquid, but not solid added sugars are positively associated with adiposity indicators cross–sectionally and a higher risk of development of impaired glucose homeostasis and insulin sensitivity over two years. Overweight/obese or glucose–intolerant children tend to have a greater susceptibility to the deleterious metabolic effects of SSB than normal–weight (BMI < 85th percentile) children or children without impaired glucose tolerance.

Our findings are consistent with most previous studies[1–13] showing that higher consumption of added sugars (either total added sugars, or merely from SSB) is linked to higher energy intake, lower consumption of essential micronutrients and lower overall diet quality in youth. The discrepancy with only two studies[14, 15] which reported no significant difference in intake of energy and micronutrient may possibly be due to their analysis using total sugars, not added sugars. To date, there was only one study in U.S. youth[16] comparing the influence on dietary intake of added sugars from liquid (SSB and sweetened dairy) and solid (pre–sweetened cereals, sweets and sweetened grains) sources. Our study agrees with the study described above and provides further evidence of added sugars from all solid sources, which as a whole is associated with a lower nutrient density in youths' diets. We did not examine each solid source of added sugars separately in our study. Although added sugars from some solid sources (e.g., fortified breakfast cereal) may be associated with a more nutrient dense diet[16], such foods only represent a small proportion of solid added sugars. In addition, our study supports the previous findings on flavoured milk (FM) and dietary intakes[17–19] that drinking FM is positively associated with intake of total milk and milk–related micronutrients (vitamin A & D). Although some other micronutrients also

showed an increasing trend with consumption of FM, it was not statistically significant in our study possibly limited by statistical power due to a relatively small number of FM drinkers and low consumption amount for those who drank FM. Considering the large variation in energy intakes with age and between sexes in children, the comparison of food and nutrients in our study was all adjusted for total energy intake. An extra analysis was performed by adjusting for total energy apart from energy intake from added sugars and the result suggested that consumption of added sugars may decrease the nutrient density by displacing other healthy foods. It is generally regarded that excessive sugar intake could be an indicator of bad diet, but those individuals with higher sugar intake usually consume more energy overall. Apart from energy contributed from added sugars per se, this extra energy either enhance or detract from the overall diet quality. Furthermore, we applied the validated Canadian Healthy Eating Index (HEI–C) score[20] as an index to evaluate the overall diet quality by comparing to the latest dietary recommendation, *Eating Well with Canada's Food Guide (EWCFG)*[21].

Previous studies examining the relationship between added sugar consumption, adiposity and weight gain in youth remain inconclusive, although the majority of evidence summarized in several review and meta–analysis articles supports a positive association[22–26]. Some intervention trials in adults have suggested the different effects on weight status from solid and liquid source of added sugars[27, 28], but most previous studies (either observational[13, 29–33] or behavioral interventional trials[34–37]) in youth studied only SSB (major liquid source of added sugars) consumption. In addition, some evidence showed the consumption of FM (the other liquid source of added sugars) is not associated with adiposity indicators[18, 19]. Very few studies examined the association between consumption of solid added sugars (from either candy or sweets) and adiposity in youth which reported either no or negative association[38, 39]. In our study, we noticed a cross–sectional association between higher added sugar intake from liquid source and greater adiposity, which is consistent with most previous evidence. We also added further evidence that such association was not observed in overall solid added

sugar intake. However, we did not observe a significant association between added sugar consumption from either solid or liquid food sources and weight gain two years later, which is similar to the findings in two longitudinal studies among Finish[39] and British[40] children. The relatively short follow–up period may be an issue and the weight gain at different stages of maturation may not be sufficiently adjusted despite the use of age/sex standardized norms. In addition, the consumption amount of SSB in our study is relatively low compared with the reported levels in U.S. youth. This may partly due to a younger age in QUALITY participants (mean aged 9.6 y at baseline), while most U.S. studies in youth include adolescents who consumed the most SSB comparing with other age groups[41]. Moreover, the dietary recall was recorded only at baseline in our study, but SSB consumption is expected to increase with age. This relatively low SSB consumption level in our study may mask the actual association with weight gain. But consumption of added sugars, particularly from SSB, may be a marker of an overall unhealthy dietary pattern and/or lifestyle, rather than a specific risk factor for weight gain[40].

Referring to the relationship with other metabolic syndrome (MetS) components, our study found that higher liquid added sugar (SSB) consumption is associated with higher systolic BP, which agrees with other two cross–sectional analyses of U.S. National Health and Nutrition Examination Survey (NHANES) data in U.S. youth[29, 42]. To date, a number of cross–sectional studies[43–46] and two short–term (12 – 16 weeks) behavioral intervention trials[47, 48] in youth have indicated a positive association between added sugar consumption and risk of prediabetes. But no longitudinal evidence yet has assessed the long–term effects on glycemic outcomes in youth. Our study provides the first evidence to show that intake of added sugars from liquid, but not solid sources predicted a higher risk of developing impaired glucose homeostasis and insulin resistance over time, independent of adiposity. In addition, some previous studies stated the adverse relationship only in overweight youth[43, 44, 49], our study provided further evidence indicating that the association with homeostasis model assessment of insulin

resistance (HOMA–IR) was more evident among overweight/obese children, comparing with normal–weight peers but was apparent in both groups. Furthermore, no study in youth yet examined the adverse health effects of added sugar consumption among youth with glucose intolerance. Our study added to current literature that the association with other MetS components was more evident in children with impaired glucose tolerance (IGT).

The strengths of this dissertation include precise, objective measurements of adiposity indicators (fat mass, by DXA), glucose homeostasis and insulin sensitivity (by oral glucose tolerance test (OGTT) and physical activity (by 7–day accelerometry) at both baseline and follow–up in a large number of children[50]. Pubertal status (Tanner stage) was also assessed to enable the adjustment for the maturation in the analysis. In addition, the detailed three 24–hour dietary recalls (including one weekend day and two weekdays) by trained dietitian and food coding in the dietary recall questionnaire enabled us to adjust for total energy intake, create food groups and estimate added sugars values from both solid and liquid food sources. Although it is better than single dietary recall, this short–term recall may still limit the reliability on long–term usual intake patterns[51]. Furthermore, there are inherent limitations with any dietary recall methodology, including underreporting[52]. Underreporting is prevalent among self–reports of dietary surveys among both youth and adult populations[53]. Specific food items particularly "unhealthy" foods rich in fat and/or added sugars (such as SSB, sweets and fast foods etc.) are more frequently underestimated during dietary recalls[54]. It is also found that underreporting increases with body mass index (BMI), but underestimation of energy intake is not confined to overweight subjects[55]. Thus, the associations demonstrated in this study may be even stronger if the dietary intake were more accurately noted. In addition, despite the relatively low consumption levels of added sugars from SSB in this study, clear associations with glycemic outcomes were present in our data. In addition, the USDA recently removed the added sugar database from its website, due to constant changes in formulations for a large number of commercial and multi-ingredient foods which primary contributed to added sugar intake to the diet. Considering the brand name

and ingredients are changed rapidly, the added sugar values were not updated at a timely base. To date, there is no other valid added sugar database. Therefore, it could be a limitation that the analysis in this thesis is mainly using this USDA database.

By the original design of the QUALITY cohort study, it is not intended to represent all Canadian children. Although the generalizability of the findings may be restricted to youth with at least one obese parent, this group comprises a substantial number of overweight/obese parents of children in the general Canadian population. In addition, recruitment from schools rather than clinics also helps to enhance the generalizability. However, volunteer bias still cannot be avoided, considering this is a health related research project, those parents motivated by health concerns are those more likely to participate. The inclusion of longitudinal data in Chapter 6 allows us to study changes over time while accounting for growth and maturation. The QUALITY cohort study is an on–going longitudinal investigation, involving rich data collection from multidisciplinary questionnaires, biological and physiological measurements for both children and parents, which provide an excellent opportunity to examine the long–term effects of added sugar consumption on metabolic health in youth. However, given the observational nature of the study, it cannot establish cause–and–effect relationship in the findings or rule out residual and unmeasured confounding despite extensive control for many important covariates. The beta-coefficients of the regression models in the first and third manuscript were relatively small compared with the normal range of those metabolic indicators. However, the calculation was based on each increase in intake of 10 g added sugar. If using the amount of 40 g (which is equivalent to 1 standard serving of SSB, 355 mL), the effect size would be 4 times higher – cross-sectionally (1.6 kg/m^2 higher in BMI, 1.2 kg greater in fat mass and 3.6 cm higher in waist circumference) and longitudinally (9.2 pmol/L higher in fasting insulin, 1.4 unit lower in Matsuda-ISI).

Future studies are encouraged to (i) examine whether reduction in consumption of added sugars in youth has beneficial effects on metabolic health in long–term behavioral intervention studies, such as nutrition education program or intervention by replacing with non-caloric sweetened beverages; (ii) examine the association between different solid sources of added sugars, dietary intake and adiposity indicators, considering not all solid added sugars exert adverse effects on diet quality and/or weight status; (iii) examine whether habits of added sugar consumption in youth are associated with dietary environment (at home, schools and community, etc.); (iv) assess whether added sugar intake co–occurs with other unhealthy lifestyle–related behavior (e.g., sedentary behaviors, smoking and alcohol drinking etc.), considering the effect may not be consumption of added sugar alone.

The findings in our study suggest that reducing added sugar intake in youth, especially from liquid sources, may be a useful strategy to enhance diet quality, mitigate the increasing risk of MetS components and thus prevent the early onset of T2DM and CVD. In addition, considering the inconsistent findings on associations with development of adiposity and other adverse metabolic outcomes, more studies on added sugar (solid vs. liquid) intake habits, including combined influence from environment (e.g. school, community and media), other dietary and lifestyle factors (e.g. sedentary behaviors), are warranted to provide further evidence on specific dietary recommendation guidelines for children and adolescents who are the highest consumers of added sugars.

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APPENDICES

Appendix 1. USDA Database for the Added Sugars Content of Selected Foods[1]

Introduction

There is growing scientific interest in the levels of added sugars in the diet, especially as it relates to research concerning the relationship between sugar intake and health and obesity prevention[2]. The Nutrient Data Laboratory has developed a Special Interest Table to provide data for the Added Sugars content of common foods, in support of nutrition research and monitoring objectives. Since there is no analytical method for distinguishing between added sugars and naturally occurring sugar, the added sugars values were calculated from sugars listed as label ingredients and nutrient values for total sugars and total carbohydrates for most processed foods. At the present time, no brand name foods are included in this table. Foods that do not contain carbohydrate, such as meats and oils, are not included. Also, foods that contain less than 2% carbohydrate and have 0 total sugars, such as most margarines and luncheon meats, are not included.

Procedures

Guidelines followed in calculating added sugars were:

- Sugars and sweeteners:
    - The sweeteners listed below were considered to be added sugars in multi–ingredient foods such as baked goods, candies, and syrup–pack fruit. (When these sweeteners are listed individually in the table, the added sugars value is zero because the sugar is intrinsic to the food. However, if users of the table use these sweeteners as ingredients in recipes to calculate the added sugar content of multi–ingredient foods or for food intake surveys, the added sugar value, Nut. No. 539, should be equal to the total sugar value, Nut. No. 269.)

        - Sugar [granulated (sucrose), brown, powdered and maple]
        - Mono– and disaccharides [e.g., fructose, lactose, maltose, glucose (dextrose)]
        - Single ingredient syrups (light corn, dark corn, high fructose corn, maple, malt, sorghum)
        - Honey
        - Molasses
        - Some ingredients such as brown rice syrup, raw sugar, liquid sucrose, invert sugar and concentrated cane juice syrup are not available in SR. Added sugars were calculated using an appropriate substitute ingredient. For example, brown sugar was substituted for raw sugar.
    - Ingredient sweeteners without carbohydrate carriers (e.g., 100% aspartame used in commercial products) were considered to contribute no added sugars to multi–ingredient foods that contained them as ingredients.
- Fruit juice concentrates:
    - If fruit juice concentrate is used as an ingredient and not reconstituted (e.g., in dry cereals, organic snack bars), the sugar it contains is counted toward added sugars.
    - If reconstituted, the sugar in the concentrate is not counted towards added sugars. For example, if canned fruit is packed in fruit juice made from reconstituted pear juice concentrate, the pear juice concentrate plus water is considered to be equivalent to single strength fruit juice and therefore is not considered to contribute to added sugars.
- Organic acids (e.g., citric acid), when used sed as food ingredients, are not counted towards added sugars.
- Sugar alcohols (e.g., mannitol, sorbitol, xylitol) are not included in added sugars.

- Oligosaccharides, such as found in corn syrup, are not included in added sugars.

Format of the Table

The table contains carbohydrate, total sugar, and added sugar values for 2,038 foods across 23 food groups. The carbohydrate and total sugar values are taken directly from the USDA National Nutrient Database for Standard Reference, release 18 (SR). Values contain the same number of decimal places as those listed in SR. Added sugars were calculated from total carbohydrate and total sugar values, using ingredient listings to identify added sugar sources. Values for added sugars are reported to one less decimal place than the carbohydrate and total sugar values from which they were derived. "Carbohydrate by difference" is determined by subtracting the sum of ash, moisture, fat and protein from 100. In food composition analysis, moisture content varies from sample to sample of the same food. Therefore, if carbohydrate by difference was determined from an analytical sample with different moisture content than that of the sample analyzed for individual and/or total sugars, the total sugars value may be slightly greater than the carbohydrate. This would be most noticeable in foods where sugar is the only carbohydrate present. In addition, individual sugars are summed to generate a total sugar value; system rounding may cause the cumulative total to exceed the carbohydrate value.

References

1. Adapted from Nutrient Data Laboratory, Beltsville Human Nutrition Research Center, Agricultural Research Service, US Department of Agriculture. USDA database for the added sugars content of selected foods. 2006. http://www.nal.usda.gov/fnic/foodcomp/Data/add_sug/addsug01.pdf

2. Dietary Guidelines Advisory Committee (DGAC). Report of the Dietary Guidelines Advisory Committee on the Dietary Guidelines for Americans. *U.S. Department of Agriculture, Agricultural Research Service.* 2005.

Appendix 2. Sources of added sugars in 24 food groups*

Sources of Added Sugars	Food Groups
Liquid	Sugar–Sweetened Beverages
	Flavoured Milk
	Fruit Juices
Solid	Dairy and Egg Products
	Spices and Herbs
	Fats and Oils
	Poultry Products
	Soups, Sauces and Gravies
	Sausages and Luncheon Meats
	Breakfast Cereals
	Fruits
	Pork Products
	Vegetables and Vegetable Products
	Nuts and Seeds
	Beef Products
	Finfish and Shellfish Products
	Legumes and Legume Products
	Lamb, Veal and Game
	Baked Products
	Sweets
	Cereals, Grains and Pasta
	Fast Foods
	Mixed Dishes
	Snacks

* based on CNF food groupings.

Appendix 3. Scoring scheme for the HEI–C (2009)[1]

Component	HEI–C	
	Maximum scores[2]	**Minimum scores[2]**
Grains (10 points)	≥ 6 servings	0 servings
Vegetables & Fruits (20 points)	≥ 6 servings	0 servings
Milk and alternatives (10 points)	≤ 1600 kcal: 3 servings 1600 – 2200 kcal: 3.5 servings ≥ 2200 kcal: 4 servings	0 servings
Meat and alternatives (10 points)	≤ 1600 kcal: 1 servings 1600 – 2200 kcal: 1.5 servings ≥ 2200 kcal: 2 servings	0 servings
Other foods (10 points)	≤ 1600 kcal: ≤ 4 servings 1600 – 2200 kcal: ≤ 6 servings ≥ 2200 kcal: ≤ 8 servings	≤ 1600 kcal: > 8 servings 1600 – 2200 kcal: >11 servings ≥ 2200 kcal: > 14 servings
Total fat (10 points)	≤ 30% of energy from fat	≥ 45% of energy from fat
Saturated fat (10 points)	≤ 10% of energy from saturated fat	≥ 15% of energy from saturated fat
Cholesterol (10 points)	< 300 mg	≥ 450 mg
Variety (10 points)	At least one serving from each food group	Failure to eat a serving from any food group
Total score	**100**	**0**

[1]Adapted from Woodruff SJ, Hanning RM. Development and implications of a revised Canadian Healthy Eating Index (HEIC–2009). *Public Health Nutr*. 2010;13(6):820–825.

[2] Individuals with servings between the minimum and maximum cut–offs are assigned a proportional score for the category.