The effect of dietary glycemic index and glycemic load on cardiovascular risk factors in school-aged children in Quebec

Karine Suissa, MSc.

Department of Epidemiology, Biostatistics and Occupational Health

McGill University

Montreal, Canada

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Table of Contents

Abstract

Background:

Unhealthy dietary intake can lead to obesity and worsened blood lipid profiles in adults and in children. Blood lipid values and obesity both track from childhood to adulthood at which time they predict cardiovascular diseases. The consumption of foods high in GI and GL are associated with cardiovascular diseases in adulthood, however not much is known about these dietary exposures in children. In addition, accurately assessing dietary intake to represent true dietary consumption is a common difficulty in nutritional epidemiology, particularly in children. Specifically, underreporting is the most common type of misreporting, which can cause information bias and affect the interpretation of diet-disease associations.

Objectives:

1) To examine the characteristics of misreporters within a cohort of children with a parental history of obesity and the bias introduced by underreporting.
2) To assess whether glycemic index and glycemic load predict cardiovascular risk factors in children after 2 years of follow-up.
3) To determine the meal-specific and cumulative effects of high glycemic index and glycemic load on 2-year cardiovascular risk factors in children.
4) To assess whether the effects of GL on blood lipids levels after 2 years in school-aged children are mediated by adiposity.

Methods:

I used data from the baseline and first follow-up visits of the QUALITY cohort which included 630 Caucasian children aged 8–10 y at recruitment with ≥1 obese parent and free of diabetes or severe illness. Child and parent characteristics were measured directly or by questionnaire. Three 24-h dietary recalls were administered by phone by a dietitian. Individual average daily and meal-specific GI and GL scores were calculated using the International Table of GI.

For objective 1, underreporters were identified using Goldberg's cutoff method to classify participants as either underreporters or acceptable reporters. Logistic regression was used to identify correlates of underreporters. For objective 2, exposures were continuous GI and GL. For

objective 3, exposures were defined as continuous meal-specific GI and GL and number of high GI as an ordinal exposure variable.

For objective 4, indicators of adiposity, including BMI z-score and percent fat mass, were the mediators of interest. A conventional approach was used as well as weighted marginal structural models to estimate the controlled direct effect between GL and blood lipids 2 years later not mediated by adiposity.

Results:

Objective 1. Underreporters were older, more likely to be female (51% vs. 43%) had a higher BMI z-score, and had poorer cardiometabolic health indicators. Parents of underreporters had a lower family income and higher BMI compared to adequate reporters. Child BMI z-score and age were the strongest correlates of underreporting. Objective 2. Average age at baseline was 9.6 years and 54.4% were male. After two-years, GL but not GI was associated with measures of adiposity (BMI z-scores and % fat mass) and blood lipids (HDL-cholesterol and triglycerides, not LDL-cholesterol), but not blood pressure. Objective 3. Dinner glycemic load was associated with an increased BMI z-score, percent fat mass, triglycerides, and decreased HDL cholesterol. Objective 4. Adiposity contributed substantially to the association between GL and TG and HDL after 2 years, and both the conventional mediation analysis method and the weighted marginal structural models did not show strong evidence of a direct effect.

Conclusion:

Underreporting of energy intake biases measurement of nutritional exposures and the assessment of exposure-outcome relations. Identifying underreporters and using an appropriate correction method is essential. Daily dietary GL predicts adiposity and blood lipids in young children after 2 years, with adiposity acting as a mediator of the associations. Glycemic load should be considered in early interventions for future cardiovascular disease prevention.

Résumé

Contexte:

Un apport alimentaire peut conduire à l'obésité et à une détérioration du profil lipidique sanguin chez l'adulte et l'enfant. La consommation d'aliments à indice glycémique (IG) élevé et à charge glycémique (CG) élevée est associée aux maladies cardiovasculaires à l'âge adulte. Cependant, on en sait peu sur ces expositions alimentaires chez les enfants. En outre, l'évaluation précise de l'apport alimentaire est un défi en épidémiologie nutritionnelle, particulièrement chez les enfants.

Objectifs:

1) Examiner les caractéristiques des individus qui font des rapports erronés de leur apport nutritionnel et décrire les biais introduits par la sous-déclaration.
2) Évaluer si IG et la CG prédisent les facteurs de risque cardiovasculaires chez les enfants après 2 ans de suivi.
3) Déterminer les effets cumulatifs et spécifiques de l'IG élevé et de la CG de chaque repas sur les facteurs de risque cardiovasculaires après 2 ans chez les enfants.
4) Examiner l'effet de l'adiposité en tant que médiateur dans l'association entre la CG alimentaire et le profil lipidique après deux ans chez les enfants.

Les méthodes:

Les données de base et de la première visite de suivi de la cohorte QUALITY ont été utilisées pour cette thèse. La cohorte QUALITY comprenait 630 enfants de race blanche âgés de 8 à 10 ans au moment de la première rencontre, avec ≥ 1 parent obèse et sans diabète ni maladie grave. Trois rappels alimentaires de 24 heures ont été administrés par téléphone par des diététistes formées. Les scores moyens individuels d'IG et de CG journaliers et spécifiques à chaque repas ont été calculés à l'aide du tableau international de l'IG.

Pour l'objectif 1, les sous-déclarants ont été identifiés à l'aide de la méthode de Goldberg afin de classifier les participants comme sous-déclarants et déclarants acceptables. La régression logistique a été utilisée pour identifier les corrélats des sous-déclarants. Pour l'objectif 2, les expositions étaient la mesure continue de l'IG et de la CG. Pour l'objectif 3, les expositions

étaient l'indice et la CG continue spécifique à chaque repas et le nombre de repas à IG et CG élevé.

Pour l'objectif 4, la cote z de l'IMC et le pourcentage de masse grasse, étaient les médiateurs d'intérêt. Une approche conventionnelle ainsi que des modèles structurels marginaux avec pondération ont été utilisé pour estimer l'effet direct contrôlé entre la CG et les lipides sanguins 2 ans plus tard, sans médiation par l'adiposité.

Résultats:

Objectif 1. Les sous-déclarants étaient plus âgés, majoritairement de sexe féminin (51% vs. 43%) avaient une cote z d'indice de masse corporelle (IMC) plus élevée et avaient de moins bons indicateurs de santé cardiométabolique. Les parents des sous-déclarants avaient un revenu familial inférieur et un IMC plus élevé par rapport au déclarants adéquats. L'âge et la cote z de l'IMC chez l'enfant corrélaient fortement avec la sous-déclaration. Objectif 2. L'âge moyen était de 9.6 ans et le pourcentage male était 54.4%. Après deux ans, la CG était associée au scores z-IMC, % de masse grasse, HDL et triglycérides. Objectif 3. La CG au dîner était associée à une augmentation du score z de l'IMC, du pourcentage de masse grasse, des triglycérides et à une diminution du cholestérol HDL. Objectif 4. Les deux méthodes d'analyse de médiation ont démontré une forte contribution de l'adiposité à l'association entre la CG et les lipides sanguins après 2 ans.

Conclusion:

La sous-déclaration de l'apport énergétique biaise l'évaluation des relations exposition-issue. Identifier les sous-déclarants et utiliser une méthode de correction appropriée est essentiel pour l'obtention de résultats valides. La CG alimentaire quotidienne prédit l'adiposité et les lipides sanguins chez les jeunes enfants après 2 ans, l'adiposité agissant en tant que médiateur de l'association. La CG devrait être prise en compte dans les interventions précoces pour la prévention future des maladies cardiovasculaires.

Acknowledgements

I am very grateful for the support I have received throughout my PhD journey. I wish to thank my thesis supervisor, Dr. Gilles Paradis, for his guidance, support, patience and devotion during my years as his student. Dr. Paradis took me on as his student the same year that he took on the role of Departmental Chair. While I knew how busy he was, he made sure I never felt it and he always managed to make time for me, for which I will be forever grateful. I also wish to thank my co-supervisor (early years) Dr. Katherine Gray-Donald who contributed greatly, with her experience and refined nutritional epidemiology expertise, to the design of my research. Even after her retirement, she made an effort to answer my questions.

I also wish to thank my statistical advisor, Dr. Andrea Benedetti, for her support and guidance, and always taking the time to discuss life. I would like to thank Dr. Melanie Henderson for her great knowledge and critical thinking that always brought me to another level of thinking when it came to my research. Committee meetings were never dull, and always involved interesting and vibrant epidemiology discussion spiced with a few jokes here and there to relieve my stress.

I am grateful for the QUALITY team, for their incessant work and devotion in managing such a large research project and to the executive committee for allowing me to be part of such an interesting project.

I am grateful for the financial support I received during my doctoral studies. I was supported by my supervisor, Dr. Paradis. I am forever thankful for your generosity. I would also like to thank Mrs. Johnson for allowing me to receive the Maysie MacSporran Graduate Scholarship. I hope that through my work and my role as a female researcher I was able to honor the name of a great woman Maysie MacSporran, showing that it is possible to be a devoted mom and a successful woman.

Finally, I cannot have pursued these doctoral studies if it weren't for my family. I am grateful for my parents, Nicole and Samy, always supportive and encouraging me throughout my several decades as a student. My siblings, Daniel, Mike and Mel, for the good laughs during

stressful times! Thank you to my wonderful daughters for their patience: Sarah who thought for all these years that I was writing Pieces and always asked how many pieces were left, just realized it was a thesis that I was writing. Lia, born right after my protocol defense, whose second word was Epidemiology. And finally, to my husband, Lionel, thank you for your love and support throughout these 12 crazy years.

Preface and Author Contribution

I was responsible for the original ideas for each manuscript presented in this thesis. I wrote the protocol for the thesis which was reviewed by all co-authors. I designed the study, carried out the statistical analyses and wrote the first drafts of each manuscript included in this thesis. The contributions of co-authors to each manuscript are described below.

Manuscript 1

Suissa K, Benedetti A, Henderson M, Gray-Donald K, Paradis G. Underreporters of energy intake have worse cardiometabolic risk profile than adequate reporters among children at risk of obesity. J Nutr. 2019 Jan 1;149(1):123-130

This manuscript was based on a series of conversations between co-authors and myself. I did all the calculations for underreporting, conducted the analyses and created tables and figure. I wrote the first draft of the manuscript which was first revised by Dr. Paradis and myself and further revised by co-authors. Dr. Paradis was central in the conception of this manuscript and clinical interpretations of results. Dr. Benedetti had an important impact on the statistical analysis. Dr. Henderson contributed significantly to the interpretation of results. All authors edited language and content of the final version of the manuscript. This study was presented as a poster at the American Heart Association EPI lifestyle conference in March 2018 and the abstract was published in *Circulation* in June 2018.

Manuscript 2

Suissa K, Benedetti A, Henderson M, Gray-Donald K, Paradis G. Effects of dietary glycemic index and load on children's cardiovascular risk factors. *Annals of Epidemiology* Oct 2019 (in press)

This manuscript was the main objective of the initial protocol of this thesis. I conducted the analysis, created tables and figure, which was followed by discussion with the co-authors. I then wrote the first draft of the manuscript that was first edited by Dr. Paradis and then sent to co-authors for further editing. All co-authors edited the final version of the manuscript. This study was presented as a poster at the American Heart Association Scientific Sessions and the abstract

was published in *Circulation* in November 2017. The manuscript has been accepted at *Annals of Epidemiology*.

Manuscript 3

Suissa K, Benedetti A, Henderson M, Gray-Donald K, Paradis G. Association of meal-specific glycemic load on 2-year Cardiovascular Risk Factors in Children

I designed the research objectives of this manuscript and conducted analyses. I conducted the statistical analyses, created the tables and wrote the first draft of the manuscript, which was followed by discussion with the co-authors. I then wrote the first draft of the manuscript that was first edited with Dr. Paradis and then sent to co-authors for further editing. All co-authors edited the final version of the manuscript. This study was presented as a poster at the American Heart Association EPI Lifestyle conference and the abstract was published in *Circulation* in March 2019. This manuscript is in preparation as of October 2019 for submission to the *American Journal of Clinical Nutrition.*

Manuscript 4

Suissa K, Benedetti A, Henderson M, Gray-Donald K, Paradis G. Empirical comparison of approaches to mediation analyses in nutrition research (submitted)

I defined the research objective and wrote the protocol which was reviewed and approved by co-authors. With the guidance of Dr. Benedetti, I conducted the analyses and created tables for the manuscript. Following a discussion with co-authors, I wrote the manuscript. Dr. Paradis edited the manuscript and made suggestions for improvement. Other co-authors then revised the manuscript. All authors edited the final version of the manuscript. This manuscript was submitted for publication in November 2019 to the *International Journal of Obesity.*

Statement of Originality

The work presented in this thesis represents an original contribution to the fields of nutritional and cardiovascular epidemiology in pediatric populations.

Accurately assessing dietary intake to represent true dietary consumption is a common difficulty in nutritional epidemiology, particularly in children. Specifically, underreporting is the most common type of misreporting, which can cause information bias and affect the interpretation of diet-disease associations. The first study presented in this thesis describes how underreporters in the QUALITY cohort had worse cardiometabolic risk profiles compared to adequate reporters. We further explored the bias caused by underreporters and different approaches for addressing these biases.

Few good quality longitudinal studies have examined the association between glycemic index and load and cardiometabolic risk factors in children. The second manuscript showed that glycemic load, but not glycemic index, was associated with higher adiposity and worsened blood lipids in children after two years. Our results highlight the important role of GL, specifically carbohydrate quality and quantity, in cardiovascular risk factors in children. Dietary recommendations for children in the prevention of obesity and CVD should focus on lowering dietary GL.

In addition, no study has assessed the meal specific effect of glycemic index and load on cardiometabolic risk factors in children, possibly due to the lack of good quality data on daily dietary consumption. The third manuscript presented in this thesis identifies an association between glycemic load at dinnertime and cardiometabolic risk factors.

Finally, no other study has examined the role of adiposity as a mediator of the associations between glycemic load and blood lipids in children. In the fourth manuscript of this thesis, we used two mediation analysis approaches to examine the role of adiposity as a mediator. We showed that adiposity is a strong mediator of the effect of glycemic load on changes in blood lipids in children.

Although I have received guidance from my committee members and co-authors on the substantive, statistical, and methodological aspects of this thesis, I declare that the conception, execution, and drafting of the work in this thesis were my own.

Statement of Support

I received financial support during my doctoral studies. I was supported by my supervisor, Dr. Paradis. I also received the Maysie MacSporran Graduate Scholarship. Data for this thesis were provided by the QUALITY cohort that is funded by the Canadian Institutes of Health Research, the Heart and Stroke Foundation of Canada and the Fonds de Recherche du Québec-Santé (FRQS). The views expressed in this thesis are mine and those of my co-authors and not from any institution that provides financial support.

List of Abbreviations

CV: cardiovascular

TG: triglycerides

HDL: high-density lipoprotein

CVD: cardiovascular diseases

LDL: low-density lipoprotein

CHO: carbohydrates

GI: glycemic index

GL: glycemic load

QUALITY: QUébec Adipose and Lifestyle InvesTigation in Youth

UR: underreporters

FFQ: food frequency questionnaire

BMR: basal metabolic rate

BMI: body mass index

EI: energy intake

PAL: physical activity level

MetS: Metabolic syndrome

SBP: systolic blood pressure

DBP: diastolic blood pressure

OR: odds ratio

MAP: mean arterial pressure

CPM: counts per minute

CDE: controlled direct effect

MSM: marginal structural models

IPW: inverse probability weights

List of Tables

List of Figures

CHAPTER 1: Introduction

Obesity is a major public health problem in children in North America with rates that have more than doubled in Canada and tripled in the United States in the past three decades.(1, 2) Between 2004 and 2013, the combined overweight and obesity prevalence in 2-17 year-old Canadians decreased but remained high at 31.4%.(1) In the United States, the prevalence of obesity in 2016 was 19.1 and 17.8% in boys and girls respectively.(2) Childhood obesity has short-term metabolic and cardiovascular (CV) effects, including increased fasting insulin and triglycerides (TG), lowered high-density lipoprotein (HDL) cholesterol and increased blood pressure. It has been associated with the development of type 2 diabetes, and hypertension in children and adolescents, and may lead to cardiovascular diseases (CVD) later in life.(3, 4) The risk of developing cardiovascular disease is higher in the presence of obesity, atherogenic lipid profiles, elevated blood pressure and diabetes, factors that are becoming more prevalent in children with time.

Atherogenic lipid profiles, including high LDL cholesterol and triglycerides, and low HDL cholesterol, increase the risk of heart disease.(5) In Canada, between 2009 and 2011, atherogenic lipid profiles were present in about 35% of people under 40 years of age.(6) The percentage of young Canadians with unhealthy LDL cholesterol was approximately 6% in the 6 to 19 year old groups.(6) As well, high blood pressure is observed in 1 in 5 Canadian adults.(7) In Canadian children and youth ranging from 2 to 17 years of age, 3.7% have a measured blood pressure that is considered borderline or elevated and this is generally observed more among overweight and obese children and youth.(1)

The increased rates of obesity, unhealthy blood lipids and blood pressure in youth are alarming from a public health perspective because of their acute effect on the health of children and adolescents and because they track into adulthood. Acquiring a better understanding of the specific causes of these cardiovascular risk factors will help in CVD prevention. Among a number of risk factors, lifestyle habits, including dietary intake and physical activity, have an important influence on CVD. High-carbohydrate diets, particularly quantity (glycemic load) and quality (glycemic index) of the carbohydrate (CHO), can lead to obesity and worsened blood lipid profiles,

which are underlying conditions of CVD and the metabolic syndrome.(8) However, data on glycemic index (GI) and glycemic load (GL) in relation to overall CV health indicators in children is limited. While the GI and GL have been positively linked to adiposity, dyslipidemia and CVD in adults,(9-13) few observational studies have assessed this association in youth, and these have reported inconsistent findings.(14-18)

In nutritional epidemiology, accurately assessing dietary intake to represent true dietary consumption is a challenge.(19) Misreporting of dietary intake, specifically under- or overreporting, is defined as a discrepancy between self-reported intake and actual food consumption.(20) Altered reporting can occur in the form of additions, omissions, substitutions, or imprecise portion sizes of foods reported which can all lead to misreporting.(20, 21) Underreporting, the most common type of misreporting in children, can be either random or systematic and in some instances it can cause information bias and affect the interpretation of diet-disease associations.(22) Research has shown differential underreporting of energy intake among overweight and obese adolescents compared to normal weight adolescents.(23) Identifying characteristics of UR is important to get a better understanding of the population being studied and to make informed methodological decisions for addressing misreporting in order to improve our interpretation of diet-disease associations.

For this thesis, I study specific aspects of diet and its consequences among children. However, before conducting this research, I address one of the major methodological challenges in nutritional epidemiology, namely the underreporting of habitual dietary intake. Specifically, I aim to assess the impact of underreporting of energy intake on risk factors for future chronic diseases among children. Then, I propose three additional research objectives.

Therefore, in the **first objective** of this thesis I describe characteristics of presumptive underreporters relative to adequate reporters and to examine relationships between reporting status and heart health indicators within a cohort of school-aged children in Quebec, Canada with a parental history of obesity

The **second objective** of this thesis was to determine how dietary GI and GL predicts (a) adiposity (b) lipid profiles and (c) blood pressure, after a two-year follow-up in school-aged children with a family history of obesity.

The **third objective** was to study the effect of meal-specific GI and GL and number of daily high GI and GL meals on cardiometabolic risk factors in school-aged children after 2 years with a family history of obesity.

The **fourth objective** was to assess whether the effects of GL on blood lipid levels after 2 years in school-aged children are mediated by adiposity, including measures of body mass index (BMI) z-score and percent fat mass.

CHAPTER 2: Literature review

2.1 Underreporting in nutritional epidemiology

2.1.1. Background

In the 1960s, before underreporting was recognized as an issue in dietary reporting, it was believed that obese individuals actually ate less than their normal weight counterparts and therefore obesity was thought to be a result of an energy expenditure defect.(19) The issue with misreporting, and specifically in this case underreporting, became more evident with the development of doubly labeled water techniques, which is currently the gold standard for calculating energy expenditure in nutrition research.(19, 24, 25)

A common difficulty in nutritional epidemiology is to accurately assess dietary intake to represent true dietary consumption.(19) Misreporting of dietary intake, specifically under- or overreporting, is defined as a discrepancy between self-reported intake and actual food consumption.(20) Additions, omissions, substitutions, or imprecise portion sizes of foods reported are different alterations in reporting that can cause misreporting.(20, 21) Underreporting, the most common type of misreporting, can be random or systematic and in some instances it can cause information bias and may affect the interpretation of diet-disease associations.(22) Research has shown differential underreporting of energy intake among overweight and obese adolescents compared to normal weight adolescents.(23) Only a handful of studies have examined characteristics of underreporters (UR) among young children(21, 26-32), several of which focused on European, Australian or Asian children, populations that are different in dietary culture and behaviors from North-American children. Identifying characteristics of UR is important to get a better understanding of the population being studied and to make informed methodological decisions for addressing misreporting in order to improve interpretation of diet-disease associations.

2.1.2. Dietary measurement tools

Several dietary measurement tools exist, including the food frequency questionnaire (FFQ), diet record and 24-hour recall.(33) The FFQ is composed of a long list of foods with a frequency table, designed to collect information about usual intake. The FFQ is relatively easy to administer, is not very costly and is not prone to interviewer bias. However, with this method, total food intake is difficult to obtain as well as actual portions and cooking methods.(33)

The diet record consists of a diary in which patients or participants record all foods and beverages consumed during a period that typically includes 3 or 4 consecutive days and never longer than 7 days to avoid respondent fatigue. The respondent must be adequately trained to provide an accurate diet record. Different measuring tools can be used to improve the precision of portion sizes, including scales and measuring cups and spoons. One great advantage of this method is that it does not require recall, if the record is filled out continuously during the day. In addition, it provides a detailed measure of food intake and meal pattern. However, it requires a certain level of commitment from the subject and a lot of work for the researcher. It can create an awareness of the subject's diet intake, resulting in an alteration of eating behaviors.(33)

The 24-hour recall consists of interviews conducted over the telephone or face-to-face in which the subject is asked to report all foods and beverages consumed in the last 24 hours.(33) The interviewers must be trained to conduct the interviews and ask about cooking methods and portion sizes. This method is less of a burden on the subject compared to the food record and captures habitual intake. The main disadvantage of the 24-hour recall is that it relies on memory. In addition, several recalls are necessary to capture a more accurate habitual intake.(33) While the 24h recall is a strong tool for the dietary measurement of usual intake, especially when conducted over three or more non-consecutive interviews, it is likely to result in some measurement error because it relies on memory and recall. In fact, studies comparing 24h recalls to observed food consumption have shown that approximately 10% of adults tend to underreport.(34) The extent of underreporting tends to vary among individuals. In a study of 524 men and women aged 30 to 69 years, reporting differed considerably according to BMI, with 7, 19 and 34% under-reporting

among the lean, normal and obese, respectively in men.(35) In women of the same BMI classifications, there was 14, 25 and 35% under-reporting of energy intake, respectively.(35)

2.1.3. Misreporting

Misreporting in nutritional epidemiology is a major concern for information bias, as we rely on subjects' ability to accurately remember and report the foods they consumed. In children, underreporting is the most common form of misreporting and is known to occur differentially among various groups of children. For example, underreporting occurs more frequently among overweight and obese adolescents.(23) In addition, the type of dietary measurement tool used also affects dietary recall.

Despite the long-standing, well established problem of dietary data underreporting, there remains a large body of published nutrition studies that do not account for underreporting.(36) In fact, only a handful of studies have examined characteristics of underreporters (UR) among young children(21, 26-32), several of which focused on European, Australian or Asian children, populations that are different in dietary culture and behaviors from North-American children. Disregarding underreporting can distort study results and greatly affect the interpretation of diet-disease associations. This resulting bias is unpredictable and depends on several factors including the magnitude of underreporting and characteristics of the population being studied.(36)

2.1.4 Goldberg's equation

The most common method for identifying misreporters is the Goldberg equation, which evaluates reported energy intake (EI) against calculated energy requirements.(37, 38) Briefly, the Goldberg method classifies participants as either UR, acceptable reporters or over-reporters by comparing reported EI to the estimated energy requirements known as the physical activity level (PAL).(32, 37) This is achieved by comparing the ratio of reported EI and calculated basal metabolic rate (EI:BMR) to a calculated lower and upper cutoff value based on the variation in

EI, BMR and PAL specific to the population being studied.(32, 37) Therefore, by definition, an EI:BMR outside of the calculated range is metabolically impossible given the EI that was reported, and these individuals would be classified as misreporters.(37)

2.1.5 Methods for correction of underreporting

Different methods of adjustment for underreporting bias have been proposed. Some authors recommend exclusion of underreporters,(19, 39) stating that underreporters tend to decrease the overall validity of a sample and failing to exclude them will likely lead to incorrect results.(39) While it is true that including underreporters will yield biased results, exclusion of underreporters is problematic. First, is the potential for introducing selection bias. Selection bias occurs when the estimates of effect in the participants, in this case only adequate reporters, differ from those in the target population, which includes both under- and adequate reporters.(40) Second, by excluding underreporters, the sample size is decreased and power to detect important associations is diminished. Third, even after excluding underreporters, there is still a risk of having underreporters in our sample depending on the cutoff used for classifying underreporters. Other methods that have been proposed to remove the effect of underreporting involve stratification of results by reporting status, adjustment for underreporting with a categorical variable and propensity score adjustment to account for all predictors of underreporting in one variable.(41) These methods have been compared, and while all agree that exclusion of underreporters likely results in selection bias, there is a lack of consensus as to which correction method is best.(41-43) Despite the limitations of each method of adjustment, it is crucial to identify underreporting bias and account for it in the analysis in order to avoid inaccurate results.

2.2. Cardiometabolic risk factors in children

2.2.1. Metabolic syndrome

Worldwide, approximately 25% of adults have the metabolic syndrome (MetS) and, recently, MetS has been more frequently observed in younger populations.(44-46) In fact, according to the Canadian Health Measures Survey, in 2009, the prevalence of MetS among children and teens was 3.5%(47) and, among the overweight and obese youth, the prevalence ranged from 29 to 50%.(8) Compared to adults without MetS, those with MetS are two to three times more likely to have a heart attack or stroke and five times more likely to develop type 2 diabetes.(48) MetS is clinically defined in adults as having three out of five risk factors including abdominal obesity, hypertension, hyperglycemia, low HDL cholesterol and elevated triglycerides.(48, 49) Risk factors for MetS comprise lifestyle habits, including smoking, physical activity and dietary intake.(46) Dietary intake has shifted in the past few decades and along with sedentary behavior has contributed to the greater prevalence of obesity and MetS among children and teens.(46, 50) The International Diabetes Federation have developed cutoffs for MetS in children, based on adult cutoffs that were modified to present more moderate values.(51) There exists a lack of consensus regarding the definition of MetS in children and several various definitions have been proposed.(52) Therefore, for the purpose of this thesis, I will focus on the components of MetS involved in CV health, including adiposity, lipid profile and blood pressure, rather than MetS as an outcome.

2.2.2. Cardiovascular health: Adiposity, lipid profile and blood pressure

Cardiovascular disease has several risk factors including smoking, obesity, atherogenic lipid profiles, elevated blood pressure and diabetes. This section provides an overview of current knowledge, definitions, measurements, diagnosis and prevalence of obesity, atherogenic lipid profiles and blood pressure in children.

Adiposity in childhood

Childhood obesity is currently among the most important public health problems and its prevalence continues to rise steadily.(53, 54) In certain developed countries, childhood obesity has attained epidemic levels.(53) Insufficient physical activity, a sedentary lifestyle and an imbalance between energy consumed and energy expended are believed to be responsible for this excessive weight gain in children.(55) Several reviews have described the effects of dietary exposures in the obesity epidemic, particularly with higher consumption of fast foods, sugar-sweetened beverages, snack foods and portions sizes.(53, 56, 57) In addition to dietary and sedentary behaviors, genetics also play an important role in a child's risk of obesity. When obesity occurs in childhood, not only does it entail several serious immediate cardiometabolic comorbidities including type 2 diabetes, elevated triglycerides low HDL cholesterol, and elevated blood pressure (54, 58), but it also tends to track into adulthood, particularly in children with a family history of obesity.(59)

Measurement of adiposity in children

Several approaches exist for measuring adiposity in children. These methods are similar to methods used in adults and the choice of method depends on the setting in which the measurement is required.(54) In clinical and epidemiological settings, measurements such as the body mass index, waist circumference, and skinfold thickness are most commonly used. In experimental research, depending on the budget available, more costly and advanced methods of measurements can be used to assess adiposity such as underwater weighing and magnetic resonance imaging. Most often, in observational studies, clinical measures are used because they are less costly, more accessible and less invasive.(53)

Body mass index is defined as a measure of weight in kilograms divided by the height in meters squared. Body mass index is widely used in diagnosing obesity in adults, however given the age and sex dependence of height in children, BMI measures are adjusted for age and sex and percentiles or z-scores are calculated.(54) While BMI is known for its limitations, including the inability to differentiate between muscle weight and body fatness, studies have reported a strong correlation between BMI percentiles scores and body fat percentages obtained using the dual x-ray absorptiometry (DEXA), particularly in children.(60)

Diagnosis and prevalence of obesity in children

Obesity in childhood is defined as an excess amount of fat.(53, 54) To determine the level of obesity in children, in 2000, the National Center for Health Statistics and Center for Disease Control published body mass index reference standards for children between the ages of 2 and 20 (table 3.1).(61) These are expressed as percentiles or z-score obtained from the CDC growth chart. There differ from other growth charts, for example the World Health Organization charts that are designed to serve as standards of growth and based on a population sample representative of universal child growth. In contrast, the CDC growth chart is based on U.S. nationally representative data.(61, 62) The main difference when comparing the WHO and CDC is in the classification of obesity. Because children in the US tend to be heavier, less children will be classified as obese using CDC standards as opposed to WHO standards.(62)

Table 2.1. Body mass index reference cutoffs for overweight and obesity in children(54)

	Percentile for age and sex	Z-score for age and sex
Overweight	BMI at or greater than 85 th to less than 95th percentile	BMI z-score at or greater than 1 to less than 2
Obese	BMI at or greater than the 95th percentile	BMI z-score at or greater than 2
Severe obesity	BMI at or greater than the 99th percentile	BMI z-score at or greater than 2.3

Abbreviations: BMI: body mass index

According to the 2007-2009 Statistics Canada Health Report, the prevalence of overweight status and obesity among Canadian children aged 2 to 17 was 26%, and since 1978, the prevalence of obesity among Canadian youth aged 12 to 17 has tripled from 3% to 9%.(63). When using the World Health Organization cut-offs for obesity and overweight in children, the prevalence was as high as 31.5% overweight and obese among Canadian children and youth aged 5 to 17, with 19.8% being considered overweight and 11.7% obese.(1) This has several short and long-term consequences as childhood obesity often tracks into adulthood, and can lead to CV and metabolic complications.(64)

Blood lipids in children

Overweight and obesity are strong predictors of lipid disorders in children.(44) Dyslipidemia is defined as abnormal levels of lipids, including cholesterol and fatty acids, or lipoproteins in the blood. The causes of abnormal blood lipids can be genetic and/or environmental, including factors such as unhealthy diet and physical activity as well as excess adiposity.(65) Due to the rising prevalence of obesity, dyslipidemia in children is becoming more frequent.(65, 66) The most common type of dyslipidemia which is mainly observed in obese children and adolescents involves elevated triglycerides, reduced HDL cholesterol and normal to slightly elevated LDL cholesterol.(65)

Diagnosis and prevalence of dyslipidemia in children

According to the 2006 Canadian clinical practice guidelines, lipid profile screenings are recommended in obese children aged 10 and older(67) in order to detect dyslipidemia and as an important step in the prevention of atherosclerosis and cardiovascular disease, with repeat testing recommended at regular intervals. Younger children may also be screened for dyslipidemia if there is a family history of premature cardiovascular disease. Recommended ranges for acceptable blood lipid levels are based on percentiles of observed blood lipids according to the Lipid Research Clinic database and are shown in table 3.2.

Table 2.2. Abnormal high blood lipid levels in boys and girls up to 18 years of age

	Abnormal (mmol/L)
HDL-C	≤0.9
LDL-C	≥2.85
TG	≥1.69

Atherogenic lipid profiles, including high LDL cholesterol and triglycerides, and low HDL cholesterol, increase the risk of heart disease in adults.(5) In Canada, between 2009 and 2011, atherogenic lipid profiles were present in about 35% of people under 40 years of age.(6) The percentage of Canadians with unhealthy LDL cholesterol was approximately 6% in the 6 to 19

year old groups.(6) According to this same survey, nine percent of children between 12 and 19 years of age and 1 to 2% of children between ages of 6 to 11 years had high triglycerides. Approximately 20% of children ages 6 to 11 had unhealthy HDL cholesterol.

Triglycerides and HDL metabolism

Low levels of HDL cholesterol have been shown in several observational studies to be associated with cardiovascular disease in adults, independent of triglyceride levels.(68)HDL cholesterol has antioxidant and anti-inflammatory properties.(69) In addition, HDL cholesterol plays a central role in lipid metabolism and cholesterol clearance. In fact, it is a carrier in the reverse cholesterol transport process, where excess cholesterol in the peripheral cells is collected and transported to the liver for removal.(70-72) Specifically, in the presence of high triglycerides, HDL cholesterol will release cholesterol esters to surrounding VLDL particles in order to bind to circulating triglycerides. As a result, HDL particles will become triglyceride-rich small HDL particles. These TG-rich HDL particles are known to have reduced antioxidant and anti-inflammatory properties. In addition, because they tend to be smaller than regular HDL cholesterol, they are catabolized more rapidly than larger HDL, consequently leading to reduced levels of circulating HDL cholesterol.(71) Thus, maintaining normal levels of triglycerides and HDL cholesterol is essential to achieve enhanced cardioprotective effects.(73)

Blood pressure in childhood

Measurement, diagnosis and prevalence of high blood pressure in children

Blood pressure is defined as the pressure exerted by the blood on the arterial walls. Blood pressure is measured in children and adults using calibrated oscillometric instruments usually validated against traditional mercury sphygmomanometers. The measurement is taken in the right arm in a seated position. Children's blood pressure measurements must be done using an instrument validated for specific age groups and with an appropriate cuff size, based on arm-circumference.(67) The definition of hypertension in children uses standardized distributions of

blood pressure in healthy children, reported as percentiles or z-scores, and accounts for differences in age, sex and height.(75) Because of the variability of blood pressure, multiple measurements at each visit are usually recommended. (76, 77)

High blood pressure cutoffs in children ages 3 to 11 years are defined in table 3.3 based on the NHLBI task force publication of "The Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents".(75)

Table 2.3. Blood pressure percentile cutoffs and classification of hypertension for children aged 3 to 11

Classification	Percentile cutoff (age, sex and height-specific)
Normal	$<90^{th}$ percentile
Prehypertension	$\geq 90^{th}$ and $<95^{th}$
Stage 1 Hypertension	$\geq 95^{th}$ and $<99^{th}$
Stage 2 Hypertension	$\geq 99^{th}$

High blood pressure is observed in 1 in 5 Canadian adults.(7) In Canadian children and youth ranging from 2 to 17 years of age, 3.7% have a measured blood pressure that is considered borderline or elevated and this is generally observed more among overweight and obese children and youth.(1)

2.2.3. Health consequences of adiposity, atherogenic lipid profile and high blood pressure in children

Obesity, abnormal lipid profiles and elevated blood pressure at a young age are all interrelated risk factors that, together, can drastically increase the risk of cardiovascular disease in adulthood. Childhood obesity is associated with several comorbidities that tend to increase with the severity of obesity.(78) The effect of obesity is widespread and affects almost every system of the body. These include the cardiometabolic system with an increased risk for hyperinsulinemia, insulin resistance, prediabetes and ultimately type 2 diabetes.(79) As well, childhood obesity results in a higher prevalence of elevated blood pressure,(80, 81) high triglycerides (44, 81, 82)

and low HDL cholesterol. The other systems that are affected by adiposity include endocrine, pulmonary, gastrointestinal musculoskeletal, psychosocial, and neurologic systems.(54) Most importantly, childhood obesity is a condition that can persist into adulthood putting the individual at an increased risk for type 2 diabetes, dyslipidemia, hypertension and atherosclerosis in adulthood.(83)

Abnormal lipid profiles in young children is highly correlated with the appearance of arterial atherosclerotic lesions in children and adolescents. While these lesions can be reversible at a younger age, when it continues into adulthood, the damage becomes irreversible.(66) Further damage can be caused in the presence of increased pressure on arterial walls resulting from high blood pressure.(66, 84) High blood pressure in childhood is also highly correlated with high blood pressure in adulthood. This relationship is even stronger in the presence of obesity. In fact, a study of children and adolescents aged 6 to 19 showed a higher prevalence of hypertension with increasing severity of obesity, specifically, a prevalence of hypertension of 9.2% was observed in severely obese children compared to 3.8% in moderately obese children.(85)

The important health effects and the complex interrelationship between these risk factors, as well as the increasing prevalence of these risk factors in young children point to the need for adequate prevention strategies in younger population.

2.3. Glycemic index and cardiometabolic risk factors

2.3.1. Carbohydrates classification and cardiovascular health

High CHO diets have long been thought to worsen CV risk factors due to postprandial hyperglycemia causing a state of oxidative stress and hyperinsulinemia.(86, 87) However, even diets low in CHO and high in fat have been associated with an increased risk of CVD in adults due to an increase in circulation of harmful triglycerides and LDL cholesterol.(88, 89) Conventionally, CHOs have been grouped together into one macronutrient group as well as classified chemically into simple and complex CHOs.(90) This classification was found to be incorrect as blood glucose responses differed greatly even within these CHO groups.(91-93) For example, starches, such as potatoes, are considered complex CHOs, however the blood glycemic response to the ingestion of potatoes is quite elevated.(93) Moreover, even simple CHOs such as sucrose and fructose have different blood glucose responses, with fructose being quite low.(90) This classification problem created the need for a more precise CHO classification based on the blood glucose response to the intake of various CHOs.

2.3.2. Glycemic index and load

Dietary GI is a concept proposed by Jenkins et al. as a means of quantifying the differences in the blood glucose response resulting from varying qualities of dietary CHO.(93) GI is defined as the incremental area under the blood glucose response curve of a 50g CHO portion of a test food relative to the response to the same amount of CHO from a standard food in the same subject.(87) The standard is usually pure glucose. White bread has also been used as a standard to compare the glucose response of different foods to that of a commonly consumed staple food, however, the CHO content of white bread is not standard for all white bread loaves, thus, it is not the most appropriate reference for the GI calculation. The units for GI represent a percentage[1] and hence range from 1 to 100 and are classified into high (≥70), medium (56-69) and low (≤55)

[1] GI is a unitless score; it represents a ratio between the value of the area under the curve of a test food divided by the average value of the areas under the curve of the reference food

groups.(94, 95) Foods such as non-starchy vegetables, legumes, and fruits have a low GI, whereas refined grain products and potatoes have a high GI (Appendix 1 shows a list of commonly consumed foods and their respective GI and GL).

GI was a novel addition to the field of nutrition. However, Willett and colleagues proposed that blood glucose response is not only a function of the CHO quality, but also of quantity. Therefore, they introduced the concept of GL, a measure of GI multiplied by the CHO content by weight (grams). They discovered that while some foods had a high GI, their GL was small, because the quantity of CHO ingested was low.(96) For example, watermelon has a relatively high GI score (~72), however, given the high water content and low CHO weight, the effect on blood glucose is not important compared to a food with a high CHO content. The GL [2] of foods has also been classified as high (≥20), medium (11-19) and low (≤10).(94, 95) Evidence on the effects of GI or GL on health outcomes is scarce especially in the context of longitudinal studies and particularly among children and adolescents.(97, 98)

2.4. Biological plausibility and scientific evidence

2.4.1. GI, GL and adiposity

Dietary GI and GL are thought to exert their harmful effects via several pathways. The consumption of high GI foods induces immediate hyperglycemia due to the quick uptake of glucose in the blood stream. This provokes a hyperinsulinemic response in order to restore normal blood glucose levels, resulting however in a hypoglycemic state. It has been suggested that this insulin-induced hypoglycemic state provokes prolonged hyperphagia, over-eating, even after normal blood glucose levels have been restored.(87, 99) Moreover, the resulting hyperphagia tends to be for high sugar, thus high GI foods, creating a cycle of hypoglycemia and hyperphagia, and resulting in weight gain and obesity.(87, 99-101) In fact, a meta-analysis of clinical trials has shown that diets of low-glycemic indices in adults are effective at lowering body fat and body mass index.(102) Following a high GI meal, there is also a suppression of free fatty acids, which

[2] GL is a unitless score, it represents the product of GI and the amount of carbohydrates (grams) divided by 100

triggers a counterregulatory hormone response to restore normal glucose levels by stimulating processes that elevate free fatty acid concentrations to levels higher than observed with a low GI diet,(93, 103, 104) leading to increased lipid accumulation in adipose tissues, to weight gain and to systemic inflammation and decreased vasodilation, all factors known to worsen CVD risk.(105, 106)

Studies that have examined the association between GI and GL and adiposity in children have reported inconsistent results. A cross-sectional study of 364 16-year-old Danish boys reported a 0.6- and 0.15-unit higher skinfold sum for each unit increase in GI and GL respectively. .(107) Three additional cross-sectional studies and one longitudinal study also found positive associations of GI and GL with adiposity in children(14, 15, 108, 109). A study of 818 British children ages 4 to 10 found a higher odds of overweight in the highest tertile of GI compared to the lowest tertile (OR:1.58; 95%CI:1.01, 2.46).(108) A study of 4,253 Italian children between the ages of 6 and 11 observed that for each 1 unit increase in dietary GI there was an 0.1 unit increase in BMI z-score.(109) A large study of 15,974 Japanese children between the ages of 6 and 11 found an increased odds of overweight in the highest vs. lowest quintile of GL in both boys (OR: 1.84; 95%CI: 1.46, 2.32) and girls (OR: 1.65; 95%CI: 1.31-2.09).(15) Meanwhile, four other cross-sectional studies have found no associations.(16-18, 110) Finally, a longitudinal study of 2,353 Australian children with a mean age of 12.7 years at baseline and who were followed for 5 years showed an increase in BMI by 0.77 kg/m^2 and in waist circumference by 1.45 cm for every 1 SD increase in dietary GL.(14) However, these associations were never observed for both GI and GL simultaneously. As well, the populations examined in these studies targeted different age groups as well as children of different ethnic origins, thus differing dietary culture.

The studies mentioned were mainly cross-sectional and had several methodological flaws, including lack of power, residual confounding, possible reverse causation, and selection bias. In addition, all of the studies stated above are subject to exposure measurement error by under-reporting of dietary intake, possibly differentially between overweight and normal weight children. Exposure measurement error may also occur due to incorrect assignment of GI values to individual foods, which would, however, likely be non-differential with respect to outcome. Furthermore, dietary data collection was done using various tools including the food frequency questionnaire

and diet records.(111) Only two studies used the 24-hour (24h) recall (the widely accepted gold standard) to collect dietary data,(16, 107) and they only used one or two days of recall, whereas the recommended number of recalls required for better accuracy of dietary data is a minimum of three non-consecutive days.

2.4.2. GI, GL and lipid profile and cardiovascular disease

Studies of adult women have shown that diets low in GI and GL have a protective effect against CVD.(87, 102) In fact, high GI diets may increase the risk for CVD through hyperglycemia-induced oxidative stress. A high GI diet leads to postprandial hyperglycemia which tends to lower circulating antioxidant concentrations and in turn induce oxidative stress. This oxidative stress is associated with increased blood pressure and accelerated blood clot formation.(87, 112-116) The higher risk of CVD may also be due to the detrimental effect that the consumption of high GI foods has on blood lipid levels.(117) Studies have supported this idea, showing that high GI and GL diets tend to, in addition to causing inflammation,(118) increase triglycerides(119) and LDL cholesterol(119, 120) and decrease HDL cholesterol.(121, 122)

There are no studies examining the association between GI and GL and lipid profile in children and only two studies have been conducted in adults. A cross-sectional study of 2941 adults observed that high GI is associated with higher levels of triglycerides (127 mg/dl in highest quintile of GI vs. 115 mg/dl in lowest quintile of GI, $p<0.001$) and lower HDL-cholesterol (47 mg/dl in highest quintile of GI vs. 49 mg/dl in lowest quintile of GI, $p<0.001$).(9) Another cross-sectional study of 141 subjects over the age of 20 examined the association between GI of foods consumed and lipid profiles as well as blood pressure. Investigators observed a consumption of foods of higher GI and GL in the highest tertile of dyslipidemia pattern, defined as elevated triglycerides and low HDL cholesterol (GI: 54.1 in tertile 1 vs. 56.5 in tertile 3, $p=0.003$; GL: 128.7 in tertile 1 vs. 147.9 in tertile 3, $p=0.026$), however they found no association between GI or GL of foods consumed and blood pressure (SBP and DBP).(123) One prospective study which assessed the association between GI and blood pressure in a younger population of 858 students who were 12 years of age at baseline and followed-up for over 5 years,(14) observed an increase in SBP (β: 1.81 mm Hg, $p=0.001$) and mean arterial pressure (MAP) (β: 1.12 mm Hg, $p=0.03$) in children that

consumed foods of higher GI (for each 1 SD [3.55] increase in GI), and higher SBP (β: 4.02 mm Hg, p=0.01), DBP (β: 2.63 mm Hg, p=0.003) and MAP (β: 3.07 mm Hg, p=0.001) in those consuming greater GL (for each 1 SD [50.89] increase in GL).

2.5. Shortcomings in the literature

Based on the literature review, there exist several knowledge gaps.

a. Most of the studies conducted were cross-sectional designs, making it difficult to assess causation and directionality of the association. Longitudinal studies are needed to identify the causal effect of GI and GL of foods consumed on CV risk factors in youth.
b. Few studies have been conducted in youth, and therefore knowledge surrounding the effect of GI and GL on CV risk factors is limited in this population. More studies of good methodological quality are needed.
c. Most studies used the food frequency questionnaire, a semi-quantitative measure, which is not the preferred method of assessing usual intake because it does not record portion sizes, among other numerous limitations. The closest method to the gold standard of direct observation and measurement of dietary consumption in nutritional epidemiology is the three non-consecutive 24h recalls.

2.6. Summary and significance

GI and GL may play a substantial role in the obesity epidemic and ensuing CV risk. Because obesity and atherosclerosis begin in childhood it is critical to understand the relationship between GI and GL with adiposity and markers of future CVD risk in children. This thesis fills an important gap in identifying the role of GI and GL in CV health in children in a longitudinal setting and provides evidence to identify targets and improve recommendations for the prevention of long-term CVD starting in pediatric subjects.

CHAPTER 3: Research objectives and hypotheses

3.1. Study rationale

The rising prevalence of obesity in children in Canada and elsewhere is a major public health concern that may have important long-term consequences for the health of the population and for future health care utilization. Childhood obesity has short-term metabolic and cardiovascular effects, including metabolic syndrome, type 2 diabetes, and hypertension, and may lead to worsened cardiovascular health indicators in youth and cardiovascular disease later in life. There is evidence to support the effect of glycemic index, a measure of carbohydrate quality, and glycemic load, a measure of carbohydrate quantity, of foods consumed on cardiovascular disease in adults. However, in children there have been very few studies to study these associations and these tend to be flawed in design and scientific methods. Understanding the role of glycemic index and load in cardiovascular health in children is important because childhood obesity is on the rise and the long-term effects on cardiovascular health are serious and can be prevented.

3.2. Main research question

In a cohort of school-aged children with a family history of obesity, do the GI and GL of foods consumed predict CV risk factors over a two-year period?

3.3. Specific objectives

1. To describe characteristics of presumptive underreporters relative to adequate reporters and to examine relationships between reporting status and heart health indicators within a cohort of school-aged children in Quebec, Canada with a parental history of obesity.
2. To determine how dietary GI and GL predicts (a) adiposity (b) lipid profiles and (c) blood pressure, after a two-year follow-up in school-aged children with a family history of obesity.

3. To study the effect of meal-specific GI and GL and number of daily high GI and GL meals on cardiometabolic risk factors in school-aged children after 2 years with a family history of obesity.
4. To assess whether the effects of GL on blood lipids levels after 2 years in school-aged children are mediated by adiposity, including measures of BMI z-score and percent fat mass.

3.4. Hypotheses

My hypotheses for each objective are that:

1. Underreporters will be different than adequate reporters and will bias results of diet-disease associations.

2. Average daily glycemic index and load will be associated with less favorable cardiovascular risk factors in children.

3. Meal-specific glycemic index and load and the frequency of high glycemic index and load meals will be associated with less favorable cardiovascular risk factors in children.

4. Average daily glycemic index and load will have direct effects on cardiovascular risk factors, independent of their association with adiposity

CHAPTER 4: Methods

4.1. Data source: QUALITY data

This thesis was conducted within the Quebec Adiposity and Lifestyle InvesTigation in Youth (QUALITY) study. The QUALITY study is an ongoing longitudinal study conducted in Quebec on children at risk for obesity and their parents. The overall objective of the QUALITY study was to study the natural history and consequences of the development of obesity in youth.(124)

4.2. Study population

QUALITY is an ongoing study of 630 Caucasian children aged 8-10 years at baseline of Western European ancestry with at least one obese biological parent (BMI >30 kg/m ^{2} or waist circumference >102 cm in men and >88 cm in women). Additionally, both biological parents had to be available to participate in the baseline assessment. The cohort was restricted to only Caucasian families to facilitate future genetic studies. Families were excluded if the mother was pregnant or breastfeeding at the baseline evaluation, or if the family had pending plans to move out of the province. Moreover, children that had any of the following criteria were also excluded: (i) a previous diagnosis of type 1 or type 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 (<600kcal/day). The first follow-up visit included 564 children (89.5% retention). The QUALITY study received ethics approval from the Ethics Boards of the Centre Hospitalier Universitaire Sainte-Justine and Université Laval.

The study cohort description states that the QUALITY cohort was not intended to be representative of the Quebec population of children aged 8 to 10. When compared to a representative sample of Quebec children of similar age, baseline characteristics of the QUALITY cohort shows a higher socio-economic status, children more likely to live with both parents, to

reside in urban regions, to be overweight or obese, to have a worse lipid profile and to report less time watching television.(124)

4.3. Recruitment and timeline

The QUALITY study recruitment consisted of distributing 400,000 flyers within 1,040 elementary schools to children in grades 2 to 5 over 3 years. The schools were located in three metropolitan areas in the Province of Quebec, namely Montreal, Sherbrooke and Quebec City. Participation was entirely voluntary where families who were interested in participating had to contact the research coordinator. A total of 3,350 families were interested in participating, of which 1,320 met the eligibility criteria for inclusion in the study. Finally, 634 children and both biological parents formed the final QUALITY cohort and participated in the baseline visit. Non-participation reasons included lack of interest in the study, one of the parents was not available to participate, the child refused to take part in the study, the family lived too far from the research centers or did not have enough available time to participate.(124)

The baseline visit occurred between July 2005 and December 2008. The follow-up visit was 2-3 years later from July 2007 to March 2011. This thesis work was a secondary analysis of the first and second visits of QUALITY.

4.4. Measurements of covariates

Detailed measurements included questionnaires for the children and the parents, biological and physiological measures of both children and parents that for children included: oral glucose tolerance test, anthropometrics (height, weight, waist circumference, skinfold thickness), and measures of body fat composition among several other measures collected. Dietary data was collected at the baseline visit, but not at follow-up.

4.4.1. Primary independent variables

Dietary data

Dietary intake data was collected by a trained dietitian within 8 to 12 weeks following the baseline visit. The dietary data collection tool used was a series of three non-consecutive 24h recalls including one weekend day at baseline and administered over the telephone. A small disposable kit of food portion models (for example, a graduated cup, a bowl, etc.) was provided to participants at the baseline clinic visit, in conjunction with a short training and practice session for both children and their parents. Interviews were unannounced and conducted with the child, and parents helped with food descriptions and cooking details when necessary. The dietary data were entered into the CANDAT Nutrient Analysis Software (Godin, London Ontario), which provides a nutrient analysis based on the Canadian Nutrition Files. A research dietitian who supervised the staff audited every tenth entry for completeness and accuracy.

The steps for assigning GI and GL to foods from the database were obtained from the literature and were done using the International table of GI(125) and if needed on GI assignments from previous studies. The steps were as follows: First we assigned a value of zero to each food group that contained less than or equal to 5 grams of CHO per 100 grams.(126) Next, we assigned a GI score from the International table to the food groups that could be found on the list. The foods that did not receive a GI value had to be assessed in terms of nutritional value by nutritionists and the 'closest match' was used to assign a GI to this food.(111, 126) By summing the scores by day and averaging the totals of the 3 dietary recalls we obtained an average daily GI and GL for each participant (Exposure variables for objective 2). Average GI and GL were obtained for each meal (breakfast, lunch, dinner) for each participant by calculating the sum of the scores of each meal by recall day and then averaging the totals of the 3 dietary recalls (Exposure variables for objective 3).

For the second objective, average daily GI and GL were assessed both as continuous variables and in tertiles as per analyses done in the literature. Since GI and GL are different parameterizations of the same concept, and therefore likely to be highly correlated, models were

created for each exposure, and GI and GL were not entered simultaneously. For the third objective, I assessed two different exposure definitions of GI and GL: 1) continuous GI or GL for each meal; 2) cumulative GI or GL during the day using the number of meals per day with a high GI (>55) or GL (≥20) score (categorical variable, ranging from 0 to 3). Skipped meals or meals with no GI/GL score were categorized as low GI and GL. Snacks were not included in the meal specific analysis due to the small number of children that reported having consumed a snack (morning snack: n=126, afternoon snack: n=170, evening snack: n=100). The fourth objective only used the continuous values of average GI and GL. The major assumption made in this study is that GI and GL are representative of usual intake during the length of follow-up because dietary data were not collected at the second visit. Although it is possible that dietary intake changes after two years of follow-up, I believe that the quality of the CHO consumed should not change significantly because dietary intake of children in elementary school, thus at ages 8 and 12, tend to generally remain under parental control. Moreover, the use of 24h recalls is believed to be the most accurate measure of usual intake involving recall compared to the other semi-parametric methods available including the food frequency questionnaire and the diet records.(111)

4.4.2. Primary dependent variables

Percent fat mass

Body fat composition, including total fat mass, percent body fat and fat distribution (upper and lower body and trunk fat masses) were assessed using a dual energy X-ray absorptiometry (DEXA, Prodigy Bone Densitometer System, DF-14664, GE Lunar Corporation, Madison, WI, USA).

Blood lipids

At each clinic visit, blood was collected from both children and parents by venipuncture following an overnight fast. Blood samples were centrifuged, aliquoted and stored at -80°C and were later analyzed in batch at the Department of Biochemistry of the CHU Sainte-Justine Hospital, a site that participates in provincial and international quality control programs and that is accredited by the International Federation of Clinical Chemistry.(124) Blood lipids, including

triglycerides, LDL cholesterol and HDL cholesterol were determined with a Synchron LX20 (Beckman Coulter) with Beckman Instruments reagents.(127)

Systolic and diastolic blood pressure

Blood pressure was measured on the right arm with the participants in the seated position, at rest for a minimum of 5 minutes. The measurement tool used for blood pressure is an oscillometric instrument (Dinamap XL, model CR9340, Critikon Company, FL, USA). The appropriate cuff size was determined by arm circumference. Five consecutive readings were recorded and the mean value of the last three readings was used for Systolic Blood Pressure (SBP) and Diastolic Blood Pressure (DBP).

Body mass index z-score

Anthropometric measurements were collected on children and parents according to a standardized protocol with participants dressed in light indoor clothing with no shoes, using a stadiometer for height (to the nearest 0.1 cm), and an electronic scale for weight (to the nearest 0.1 kg). Height and weight measures were taken twice, and if the first two measures differed by 0.2 centimeters or 0.2 kilograms or more, a third measure was taken. The final value was the average of the two closest measurements. BMI was calculated as weight in kilograms divided by height in meters squared. Age- and sex-specific BMI z-score was obtained using CDC growth charts.(128)

4.4.3. Covariate and confounding variable measurement

Physical activity

Physical activity was measured objectively using 7-day accelerometry (Actigraph LS 7164 activity monitor, Actigraph LLC, Pensacola, FL, USA) in the week following the baseline clinic visit. Accelerometry data were downloaded as 1-min epochs and underwent standardized quality control and data reduction procedures;(129) participants with a minimum of four or more days with a minimum of 10 hours of wear time were retained for analyses. Moderate to vigorous physical activity was computed by adding the total minutes spent daily in moderate and in vigorous physical activity and averaging over the total number of valid days of wear.(130) We used average

counts per minute (CPM) as the physical activity variable, calculated as the total number of activity counts divided by total wear time in minutes.

Pubertal status

Sexual maturity was observed by trained nurses and scored according to the Tanner stages.(131, 132) For our analyses, we categorized children into prepubertal (stage 1) or pubertal (stages 2 and higher).

Parental information

Parental reports on the highest maternal and paternal education level obtained as well as household income were collected. As well, family history of disease was also collected from parental reports.

Underreporting

Misreporting of dietary intake, specifically under- or overreporting, is defined as a discrepancy between self-reported intake and actual food consumption and is a result of additions, omissions, substitutions, or imprecise portion sizes of foods reported.(20, 21) For this thesis, I used the Goldberg equation(37) to evaluate misreporting. The most common method for identifying misreporters is the Goldberg equation, which is based on the concept of energy-in equals energy-out, thus evaluates reported energy intake (EI) against calculated energy requirements.(37, 38) The Goldberg equation calculates confidence limits within which we can identify adequate reporters, as well as under- and overreporters, which evaluates whether the mean reported EI is plausible given the child's energy expenditure.(37) The Goldberg equation requires the input of values of physical activity level (PAL) and basal metabolic rate (BMR) with their respective coefficients of variation, and a within-subject variation in energy intake (EI). For the QUALITY cohort population of children, I obtained values required for the Goldberg equation from published literature.(37, 133, 134) Specifically, I used a PAL of 1.65, which represents a conservative value of physical activity for children(133), with a total variation in PAL of 15.(37, 135) I calculated individual BMR using the Schofield equation, which has the best agreement with actual measurement (using indirect calorimetry),(134) with a coefficient of variation of 8.5.(37) The within-subject variation in EI was 23.(37) Finally, The ratio of EI to

BMR (EI:BMR) for each individual was compared to the 1.11 cutoff, below which an individual would be considered an underreporter and upper cutoff value was 2.46 above which one would be considered an overreporter.

CHAPTER 5: Statistical analysis

5.1. Analysis

Descriptive statistics were used to describe characteristics of participants at baseline. For each objective, we analyzed outcomes measures as continuous variables. We used univariate and multivariate linear regressions to examine the association between exposure variables and outcome measures. Separate models were created for each dependent variable and glycemic index and load as independent variables. The potential covariates considered in our models were: age, sex, pubertal status, family income, parental education, fat and protein intake (residuals), season and underreporting, measured at baseline. All dietary variables (except glycemic index) were adjusted for energy intake using the residual method.(34) We used multiple imputation (Proc MI in SAS 9.3, and ICE in STATA version 13) to account for missing data of covariates, particularly the physical activity variable that had 15 percent missing data. Age and sex were not included in the BMI z-score, SBP z-score and DBP z-score models because these outcome measures are already adjusted for age and sex. We assessed linearity with adjusted linear regression splines of predicted BMI z-score, percent fat mass, TG, LDL, HDL, SBP z-score and DBP z-score as a function of GL which showed nearly linear relationships between GL and outcomes of interest, therefore estimates of linear regressions are presented. We tested for interactions between each exposure variables (GI and GL) and sex and with BMI category (under/normal weight vs. overweight/obese) by introducing an interaction term one at a time in adjusted models. We used SAS version 9.3 for analyses of objectives 1, 2 and 4 and STATA version 13.1 for objective 3 and graphics.

5.1.1. Goldberg's equation

Calculation of ratio of energy intake to estimated energy requirements and cutoff for underreporters using the Goldberg equation

The values used for the Goldberg equation(38) were derived as follows: to calculate individual basal metabolic rates (BMR), I used the Schofield equation with weight and height which has a coefficient of variation (CV_{wB}) of 8.5;(37) the physical activity level (PAL) that I

used was 1.65 which is considered moderate PAL in boys and girls ages 8 to 10,(133) with a coefficient of variation (CV_{tP}) of 15 as suggested by Black for the Goldberg equation,(37) and the within-subject variation in energy intake (CV_{wEI}) of 23.(37) Individuals with a EI:BMR ratio below a cutoff of 1.11 were considered underreporters while those with values above 2.46 were considered overreporters. Only 2 participants were overreporters which we chose to include in the adequate reporters since excluding these 2 participants did not change our results.

Goldberg's equation

$$EI_{rep}:BMR > PAL \times \exp\left[s.d._{min} \times \frac{(S/100)}{\sqrt{n}}\right] \qquad S = \sqrt{\frac{CV_{wEI}^2}{d} + CV_{wB}^2 + CV_{tP}^2}$$

Values used for the calculations of confidence limits

EI:BMR : Ratio of energy intake and calculated BMR

CV_{wB}=8.5 (the coefficient of variation of repeated BMR measurements for Schofield)

CV_{wEI}=23 (the within-subject coefficient of variation in energy intake, 23 is the pooled within-subject variation coefficient recommended)(37)

CV_{tP}=15 (the total variation in PAL)(37)

PAL= 1.65

Calculated cutoff values:

Underreporter: EI:BMR ≤ 1.11

Overreporter: EI:BMR >2.46

Table 5.1. Schofield (WH: weight-height) equation for calculation of basal metabolic rate (134)

Gender	Equation
Male	BMR = 19.6 * Wt + 130.3 * Ht + 414.9
Female	BMR = 16.97 * Wt + 161.8 * Ht + 371.2

Abbreviations weight: Wt; height: Ht

Calculated using baseline weight and height because dietary data was only available at baseline

5.1.2. Mediation analysis

We assessed mediation by adiposity (BMI z-score and percent fat mass) with the conventional Baron and Kenny method.(136) First, we estimated the total effect of GI and GL on TG and HDL on the additive scale (note that X hereby denotes both GI and GL and Y hereby denotes different outcomes including TG and HDL). To this end, we regressed Y_i on X_i and confounders (C_i) as such:

$$E[Y|X,C] = \beta_0 + \beta_1 X_i + \beta_2 C_i \qquad \text{(Model 1)}$$

β_1 from model 1 will be the estimate of the total effect provided that the measured confounders are sufficient to control for the confounders of the X-Y relation. Second, we estimated the direct effect of X on Y using the conventional approach described by Baron and Kenny.(136) For this, we regressed each outcome Y on X, C and adiposity (the mediator M) by fitting a linear regression model as such:

$$E[Y|X,C,M] = \beta_0 + \beta_1 X_i + \beta_2 C_i + \beta_3 M_i \qquad \text{(Model 2)}$$

β_1 from model 2 will be the estimate of the direct effect of X that is not mediated through M, provided that the measured confounders that are adjusted for are sufficient to control for the confounders of the relation between X and Y. Third, we tested for interaction by including interaction terms between X and M in model 2, and because these terms were not statistically significant they were dropped from the model. Fourth, we compared traditional mediation analysis results with result obtained using MSM and IPW. For this, we computed the controlled direct effect (CDE) using a weighted linear MSM, a weighted generalized estimating equation, an approach proposed by VanderWeele(137) and Valeri(138) for continuous exposure, mediators and outcomes.(139) The following model was fitted:

$$g(\mu) = \beta_0 + \beta_1 X_i + \beta_2 M_i + \beta_3 A_i M_i \qquad \text{(Model 3)}$$

where g is a monotone link function. In this case, the continuous outcome followed a linear link function. Inverse probability weights were used to balance covariates and hence control for confounding between X and Y and M and Y. Weights were constructed for both exposure variables (glycemic index and glycemic load) and the mediators (continuous BMI z-score and percent fat mass). We used stabilized weights, which are preferred to standard weights because they are considered more stable; and because of the continuous nature of X and M, unstabilized weights would have infinite variance.(140) For the continuous exposure and mediator variables we used the marginal average density function of X in the numerator and the marginal density function of X conditional on C as the denominator for the X-Y weights and repeated the same method for the M-Y weights.(140) The product of the two stabilized weights calculated were used in the MSM.

The CDE for a change in exposure from level x^* to level x will be obtained as follows with estimates from the final weighted model [3]:

$$CDE = (\beta_1+\beta_3 m)(x- x^*)$$

The CDE measures how much the mean of the outcome would change if the mediator were controlled at level m uniformly in the population, but the exposure were changed from level x^* to level x. Although sometimes unrealistic, a requirement for the CDE is that an intervention be effective at setting every subject to having the same value of the mediator. In general, m would be set as the mean BMI z-score in the study sample. For the purpose of this study, CDE was equal to β_1 because the interaction term β_3 was not significant. We used SAS version 9.3 for analyses.

5.2. Power: Minimal detectable slopes

Since this was a secondary analysis of an ongoing cohort study, I calculated the minimal detectable slope with a fixed sample size of 600, a power of 80% and a type 1 error of 0.05. From the literature, I obtained standard deviations for GI and GL in children, as well as for outcome variables (BMI, percent body fat, triglycerides, HDL and LDL cholesterol, SBP and DBP). For

objectives 2 and 3, lowest and highest minimal detectable slopes for GI as an exposure ranged from 0.011 to 0.576 for HDL and SBP respectively, and for GL they ranged from 0.001 to 0.038. (Detailed calculations presented in appendix 2) This indicates that depending on the SD in the population, there might be insufficient power to detect a smaller association with certain outcomes, namely HDL cholesterol and SBP. For objective 4, the weighting required for the marginal structural model typically increases the variability in the exposure, thereby decreasing power.

5.3. 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. For this secondary analysis, ethics approval was obtained from McGill University Faculty of Medicine Ethics Committee (Appendix 1). Data is safeguarded at the Sainte-Justine Hospital and distributed to principal investigators through special written requests and all data is kept fully anonymous at all times.

CHAPTER 6: Energy underreporting in the QUALITY cohort

This manuscript was completed to shed a light on underreporting of energy intake in children, an area with scarce research, and to document the resulting bias in nutritional epidemiology. No previous study has examined the characteristics of underreporters in a population of children at risk for obesity. This work was published in *Journal of Nutrition* in 2019:

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Suissa K, Benedetti A, Henderson M, Gray-Donald K, Paradis G. The Cardiometabolic Risk Profile of Underreporters of Energy Intake Differs from That of Adequate Reporters among Children at Risk of Obesity. *J Nutr*. 2019 Jan 1;149(1):123-130

MANUSCRIPT 1

Underreporters of energy intake have worse cardiometabolic risk profile than adequate reporters among children at risk of obesity

Karine Suissa, MSc[1], Andrea Benedetti, PhD[1,2,3], Mélanie Henderson, MD, PhD[4,5], Katherine Gray-Donald, PhD[6], Gilles Paradis, MD, MSc[1]

Affiliations:

[1]Department of Epidemiology, Biostatistics, and Occupational Health, McGill University, Montreal, Quebec, Canada

[2]Department of Medicine, McGill University, Montreal, Quebec, Canada

[3]Respiratory Epidemiology and Clinical Research Unit, McGill University Health Centre, Montreal, Quebec, Canada

[4]Research Center of Centre Hospitalier Universitaire Sainte-Justine, Montreal, Canada.

[5]Department of Pediatrics, Faculty of Medicine, Université de Montréal, Montreal, Canada.

[6] School of Dietetics and Human Nutrition, McGill University, Montreal, Quebec, Canada (retired)

Corresponding author:

Gilles Paradis, MD, MSc, FRCPC

Professor and Chair

Department of Epidemiology, Biostatistics and Occupational Health

McGill University - Purvis Hall

1020 Pine Avenue West

Montreal, Quebec, Canada

Tel.: 514-398-6258

Fax: 514-398-2373

Email: chair.epid@mcgill.ca

Author's last names: Suissa, Benedetti, Henderson, Gray-Donald, Paradis

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Abbreviation list:

AR adequate reporters, **BMR** Basal Metabolic Rate**, DBP** Diastolic Blood Pressure, **EI** energy intake, **EI:BMR** ratio of energy intake and basal metabolic rate, **PAL** physical activity level, **QUALITY** QUébec Adipose and Lifestyle InvesTigation in Youth, **SBP** Systolic Blood Pressure, **UR** underreporters

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ABSTRACT

Background: Misreporting of energy intake (EI) in nutritional epidemiology is a concern for information bias and tends to occur differentially in obese versus non-obese subjects.
Objective: We examined characteristics of misreporters within a cohort of children with a parental history of obesity and the bias introduced by underreporting.
Methods: The QUALITY cohort included 630 Caucasian children, 8-10 years at recruitment having at least one obese parent (body mass index (BMI)>30kg/m2 or waist circumference:>102 cm [men], >88 cm [women]) and free of diabetes or severe illness. Children on anti-hypertensive medications or following a restricted diet were excluded. Child and parent characteristics were measured directly or by questionnaire. Three 24-hour dietary recalls were administered by phone by a dietitian. Goldberg's cut-off method identified underreporters (UR). Logistic regression identified correlates of UR. We compared coefficients from linear regressions of BMI after 2 years on total EI at baseline in 1) all participants; 2) adequate reporters (AR) (excluding UR); 3) all participants statistically adjusted for underreporting; 4) excluding UR using individual physical activity level (PAL) specific cutoff; 5) statistically adjusted for underreporting using PAL specific cutoffs.
Results: We identified 175 UR based on a calculated cut-off of 1.11. UR were older, had a higher BMI z-score and poorer cardiometabolic health indicators. Parents of UR had a lower family income and higher BMI. Child BMI z-score (OR:3.07, 95%CI:2.38-3.97) and age (OR:1.46 per year, 95%CI:1.14-1.87) were the strongest correlates of underreporting. The association between BMI and total EI was null in all participants but became significantly positive after excluding UR (ß=0.62 per 1000 kcal, 95%CI:0.33-0.92) and after adjustment for UR (ß=0.85 per 1000 kcal, 95%CI:0.55-1.06).
Conclusions: UR in 8-10 year-old children differed from AR. Underreporting biases measurement of nutritional exposures and the assessment of exposure-outcome relationships. Identifying UR and using an appropriate correction method is essential.
Keywords: Cardiometabolic risk, glycemic index, glycemic load, adiposity, body mass index, energy intake, underreporting, 24-hour recall, misreporting, children

INTRODUCTION

A common difficulty in nutritional epidemiology is to accurately assess dietary intake to represent true dietary consumption.(1) Misreporting of dietary intake, specifically under- or overreporting, is defined as a discrepancy between self-reported intake and actual food consumption.(2) Additions, omissions, substitutions, or imprecise portion sizes of foods reported are different alterations in reporting that can cause misreporting.(2, 3) Underreporting, the most common type of misreporting, can be random or systematic and in some instances it could cause information bias and may affect the interpretation of diet-disease associations.(4) Research has shown differential underreporting of energy intake among overweight and obese adolescents compared to normal weight adolescents.(5) Only a handful of studies have examined characteristics of underreporters (UR) among young children(3, 6-12), several of which focused on European, Australian or Asian children, populations that are different in dietary culture and behaviors from North-American children.

Identifying characteristics of UR is important to get a better understanding of the population being studied and to make informed methodological decisions for addressing misreporting in order to improve our interpretation of diet-disease associations. The most common method for identifying misreporters is the Goldberg cutoff, which evaluates reported energy intake (EI) against calculated energy requirements.(13, 14) Briefly, the Goldberg method classifies participants as either UR, acceptable reporters or over-reporters by comparing reported EI to the estimated energy requirements known as the physical activity level (PAL).(12, 13) This is achieved by comparing the ratio of reported EI and calculated basal metabolic rate (EI:BMR) to a calculated lower and upper cutoff value based on the variation in EI, BMR and PAL specific to the population being studied.(12, 13) Therefore, by definition, an EI:BMR outside of the calculated range is metabolically impossible given the EI that was reported, and these individuals would be classified as misreporters.(13) While doubly labeled water remains the gold standard for assessing reporting error, it is costly and thus not always available. The Goldberg equation is based on population estimates and therefore not as definite, however remains a valuable method to use when more precise measures are not available.

The objective of this study was to describe characteristics of presumptive underreporters relative to adequate reporters and to examine relationships between reporting status and heart health indicators within a cohort of school-aged children in Quebec, Canada with a parental history of obesity, and discuss potential bias on analyses.

SUBJECTS AND METHODS

Study population

We used baseline (July 2005 to December 2008) and follow-up (July 2007 to March 2011) data from the QUébec Adipose and Lifestyle InvesTigation in Youth (QUALITY) cohort participants which was originally designed to study the natural history and consequences of the development of obesity in youth.(15) Briefly, QUALITY is an ongoing study of 630 Caucasian children aged 8-10 years at baseline of Western European ancestry with at least one obese biological parent (body mass index (BMI) >30 kg/m$_2$ or waist circumference >102 cm in men and >88 cm in women). Additionally, both biological parents had to be available to participate in the baseline assessment. The cohort was restricted to only Caucasian families to facilitate future genetic studies. Families were excluded if the mother was pregnant or breastfeeding at the baseline evaluation, or if the family had pending plans to move out of the province. Moreover, children that had any of the following criteria were also excluded: (i) a previous diagnosis of type 1 or type 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 (<600kcal/day). The first follow-up visit included 564 children (89.5% retention). The QUALITY study received ethics approval from the Ethics Boards of the Centre Hospitalier Universitaire (CHU) Sainte-Justine and Université Laval.

Detailed measurements included questionnaires for the children and the parents, biological and physiological measures including oral glucose tolerance test, anthropometrics (height, weight, waist circumference, skinfold thickness) of both children and parents, and measures of body fat composition among several other measures collected.(15) Parental reports

on the highest maternal and paternal education level obtained, household income and family history of disease were collected.

Measurements

Anthropometric measurements were collected according to a standardized protocol with participants dressed in light indoor clothing with no shoes, using a stadiometer for height (to the nearest 0.1 cm), and an electronic scale for weight (to the nearest 0.1 kg). Height and weight measures were taken twice, and if the measures differed by 0.2 centimeters or 0.2 kilograms or more, a third measure was taken. The final value was the average of the two closest measurements. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared.

Percent body fat was assessed using dual energy X-ray absorptiometry (DXA, Prodigy Bone Densitometer System, DF-14664, GE Lunar Corporation, Madison, WI, USA). Blood was collected from both children and parents by venipuncture following an overnight fast. Blood plasma samples were centrifuged, aliquoted and stored at -80°C and were later analyzed in batch at the Department of Biochemistry of the CHU Sainte-Justine Hospital, a site that participates in provincial and international quality control programs and that is accredited by the International Federation of Clinical Chemistry.(15) Blood lipids, including triglycerides, LDL cholesterol and HDL cholesterol were determined with a Synchron LX20 (Beckman Coulter) with Beckman Instruments reagents.(16) Blood pressure was measured on the right arm with the participants in a seated position, at rest for a minimum of 5 minutes using an oscillometric instrument (Dinamap XL, model CR9340, Critikon Company, FL, USA) and an appropriate cuff size determined by arm circumference. Five consecutive readings were recorded and the mean value of the last three readings was used for Systolic Blood Pressure (SBP) and Diastolic Blood Pressure (DBP).

Physical activity was measured objectively using 7-day accelerometry (Actigraph LS 7164 activity monitor, Actigraph LLC, Pensacola, FL, USA) in the week following the baseline clinic visit. Accelerometry data were downloaded as 1-min epochs and underwent standardized quality control and data reduction procedures;(17) participants with a minimum of four or more

days with a minimum of 10 hours of wear time were retained for analyses. Moderate to vigorous physical activity was computed by adding the total minutes spent daily in moderate and in vigorous physical activity and averaging over the total number of valid days of wear.(18) We used average counts per minute (CPM) as the physical activity variable, calculated as the total number of activity counts divided by total wear time in minutes.

Dietary data

Dietary intake was assessed 8 to 12 weeks following the clinic visit using three non-consecutive unannounced 24-h recall interviews including one weekend day administered over the phone by trained dietitians. Complete dietary data was obtained for 613 participants. A small disposable kit of food portion models was provided to participants at the baseline clinic visit, in conjunction with a short training and practice session for both children and their parents. Interviews were conducted with the child, but parents were asked about food description and cooking details when necessary. The dietary data were entered into the CANDAT Nutrient Analysis Software (Godin and associates, London, Ontario, 2007), which provides a nutrient analysis based on the Canadian Nutrition Files.(19) A research dietitian who supervised the staff audited every tenth entry for completeness and accuracy.

Statistical analysis

The Goldberg equation(13) was used to evaluate misreporting. The confidence limits were calculated from the Goldberg equation as described by Black(13) to determine if the mean reported EI is plausible. The Goldberg equation includes values of PAL and BMR and coefficients of variation for both, and a within-subject variation in EI which we obtained from our data and from the published literature. For our population, PAL was defined as 1.65 which is a conservative value for children.(20) The Schofield equation was used for calculating BMR, which has the best agreement with actual measurement, with a coefficient of variation of 8.5.(13) The within-subject variation in EI was 23.(13) Finally, the total variation in PAL was 15.(13, 21) The ratio of EI to BMR (EI:BMR) for each individual was compared to the 1.11 cutoff, below which and individual would be considered an underreporter and upper cutoff value was 2.46

above which one would be considered an overreporter. Only 2 participants had an EI:BMR above 2.46, and given that no difference in results was observed after excluding these 2 participants, we chose to include them in the adequate reporter (AR) group. For our sensitivity analysis, we also calculated PAL-specific cutoffs for each participant using individual PAL values which were calculated using available accelerometer data (n=535) to classify children into three physical activity groups based on recommendations of 60 minutes per day of moderate to vigorous physical activity (sedentary: less than 30 minutes per week, moderate: 30 to 60 minutes, and active: more than 60 minutes). We assigned PAL values of 1.45 for sedentary, 1.65 for moderate and 1.9 for active.(20) These PAL specific cutoff values were used to identify UR.

We compared UR and AR among all participants and separately for boys and girls, and by BMI category (under- and normal weight vs. overweight and obese). T-tests and chi-square tests were used for these comparisons, with a P-value<0.05 to indicate significance. We used logistic regression to identify correlates of UR. We examined the bias resulting from underreporting by comparing the coefficients from the linear regression of BMI z-score at 2 years of follow-up on total EI at baseline in 1) all participants, 2) the AR subset, after excluding UR using an overall PAL of 1.65 (cutoff 1.11), and 3) all participants after statistical adjustment for underreporting using an overall PAL of 1.65 (cutoff 1.11). As a sensitivity analysis, we repeated analyses 2 and 3 above using the PAL-specific cutoffs calculated for individuals with complete accelerometer data. As secondary analysis, we examined the effect of underreporting on energy-adjusted carbohydrate, protein and fat using energy densities within the 5 population subsets used in the main bias analyses. We also used restricted cubic splines to examine different dietary exposure-outcome associations with flexible modeling and results are shown graphically. STATA version 13 and SAS version 9.3 were used for the analyses.

RESULTS

A total of 630 children aged 8-10 years were assessed at baseline (Figure 6.S1: see the supplementary material associated with this article online), of which 613 participated in the dietary interviews. Using the calculated Goldberg cutoff of 1.11, we identified 175 UR. In bivariate analyses, underreporters and AR differed substantially (Table 6.1). Overall, UR had

worse cardiometabolic health than AR, including a higher BMI, with a much higher percentage being obese compared to the AR (37.1% vs. 3.2%). Systolic and diastolic blood pressure and triglycerides and LDL cholesterol were significantly higher in UR and HDL cholesterol was lower. Underreporters were also older and less physically active than AR. The overall average EI:BMR was 1.32 and ranged from 0.39 to 2.54. The mean EI:BMR in UR and AR was 0.93 and 1.49 respectively (data not shown). Underreporters reported a diet that contained less carbohydrate, fewer snacks and lower overall EI than AR, as well as fewer servings of all four food groups (Table 6.2). In addition, underreporters reported lower calcium and vitamin D and greater sodium intake per 1000 kcal than adequate reporters (Table 6.3). Parents of UR had a lower family income and a higher BMI than parents of AR (Table 6.1 & Table 6.S1: see the supplementary material associated with this article online).

In multivariable logistic regression, age (OR: 1.46 per year, 95%CI: 1.14-1.87), and BMI z-score (OR: 3.07, 95% CI: 2.38-3.97) were the only significant correlates of underreporting (Table 6.3). Linear regressions showed no association between BMI at 2-year follow-up and total baseline EI when all participants were included but became significantly positive (ß=0.62 per 1000 kcal, 95%CI: 0.33-0.92) after exclusion of the UR and when adjusted for underreporting in the model (ß=0.80 per 1000 kcal, 95%CI: 0.55-1.06) (Figure 6.1A). Results were similar when using PAL specific cutoffs.

In our secondary analysis, linear regressions of energy-adjusted carbohydrate (Figure 6.1B), protein (Figure 6.1C) and fat (Figure 6.1D) showed no association with BMI z-score in unadjusted and adjusted models for underreporting.

In stratified bivariate analyses, results were similar when stratified by sex (Table 6.S2). Within categories of obesity, the only significant differences observed between UR and AR were age and BMI (Table 6.S3). Underreporters were older, had a higher BMI and were predominantly female compared to AR.

Multivariate regression splines of glycemic load and BMI z-score show a change in shape when UR are excluded from the analyses compared to when all participants are included.

Including UR pulls the left side of the curve up resulting in a shape that tends to be flat. The same phenomenon is observed with other cardiometabolic risk factors (Figure 6.2-6.4).

DISCUSSION

Using data from the QUALITY study, we identified characteristics of EI underreporters in a sample of school-aged children at risk for obesity. Goldberg's cutoff is a commonly used method to identify misreporters. This cutoff varies between studies depending on the variation coefficient used for EI, BMR equation and PAL level. For this reason, the proportion of under- and over-reporting is not easily comparable from one study to another and is only possible with a study that uses similar coefficients. Farajian et al. used a cutoff interval of 1.09 to 2.21 in Greek children ages 10 to 12 and identified 36% of UR and 16% overreporters.(11) Lioret et al. classified 26% of their groups of children from France ages 11 to 17 as UR, but found no overreporters.(9) The 29% of UR identified in our sample seems reasonable for the QUALITY cohort children who are at high risk for obesity. Other studies have used lower cutoff values, often because they selected a PAL at or below 1.55. The PAL of 1.65 used in our analysis is the estimated required level of moderate physical activity for this age group suggested by the Food and Agriculture Organization of the United Nations in collaboration with the World Health Organization and the United Nations University.(20) Using a PAL of 1.55 or lower to indicate a sedentary lifestyle is insufficient in children and may result in an underestimation of UR.(12)

According to the most recently published 2015-2020 Dietary Guidelines for Americans,(22) children between the ages of 8 and 10 should consume between 1,600 and 1,800 kcal. In our cohort, AR and UR reported an energy intake of 1,822 kcal and 1,348 kcal respectively, resulting in a 474-kcal deficit for UR compared to AR. An energy deficit of 500 kcal/d should result in 0.45 kg of weight lost per week,(23) however, our UR had higher BMI. Underreporters and AR reported similar proportions of their energy intake from carbohydrates, but UR had lower proportion of fat and slightly higher proportion of protein, however, these were all within normal recommended ranges of macronutrient consumption. Studies of macronutrient distributions in UR adults have reached conflicting conclusions, one study finding differential reporting of all macronutrients between UR and AR(24) and another study finding no

difference.(25) Also, contrarily to another study that found no difference of energy-adjusted micronutrients between UR and AR, we observed lower calcium and vitamin D and higher sodium intake per 1000 kcal.(26)

In our study, UR were older, more likely to be girls and had a higher BMI compared to AR, consistent with other studies in adults(1) and most studies in children and adolescents,(5-7, 10, 11, 27-33) but not all.(34-36) BMI is recognized as the strongest predictor of underreporting.(1) It is not clear why obese individuals tend to underreport more than leaner individuals, but possible explanations include intentionally misreporting actual food intake, possibly due to social desirability or social approval biases, more frequent dieting compared to leaner individuals, or other factors.(37) Children that follow a strict diet regiment may be classified as UR because of their low EI when they are actually accurately reporting their intake, which may result in misclassification of UR. In the QUALITY cohort, children on a restricted diet were excluded from the cohort, thereby reducing potential misclassification due to dieting.(15) Parents of UR had a higher BMI and lower family income than parents of AR, consistent with another study that observed an association with income.(38)

In addition to being heavier, UR had worse cardiometabolic risk factors than AR. Specifically, blood pressure and LDL cholesterol levels were higher and HDL cholesterol lower in UR than in AR. These results are similar to the only other study that reported on biochemical parameters, including LDL and HDL cholesterol and triglycerides, of UR in a small and underpowered sample of 96 South American adolescents.(39)

When assessing dietary intake in relation to disease outcomes, UR tend to agglomerate in the upper left quadrant of a graph (Table 6.S4), pulling the left side of the regression up. Including these participants tends to shift the slope of a positive association towards either a null association or possibly an inverse association. To address underreporting bias, different methods have been proposed. Some authors recommend exclusion of UR to avoid spurious results,(1, 40) however, exclusion of UR may be problematic. First, the potential for selection bias which occurs when the estimates of effect in the participants, in this case only AR, differ from those in the target population, which includes both UR and AR.(41) Second, by excluding UR, the

sample size is decreased and power to detect associations is diminished. Third, a number of false negatives may remain after excluding UR, depending on the cutoff used. Other methods that have been proposed involve stratification of results by reporting status, statistical adjustment for underreporting and propensity score adjustment to account for all predictors of underreporting.(42) Although, it is clear that exclusion of UR results in selection bias, there is a lack of consensus as to which correction method is best.(42-44) Despite the limitations of each method, it is crucial to account for UR in the analysis in order to avoid biased results.

Our secondary analysis showed that energy-adjusted nutrients were not associated with BMI z-score, regardless of underreporting. This could indicate that energy-adjustment addresses the issue of underreporting when examining associations of diet composition exposures with disease outcomes (45). However, we cannot assume that all macronutrients are underreported to the same extent given that some individuals may be more reluctant to report certain macronutrients.(46, 47) Our results show that percent energy from fat and protein differed between UR and AR and therefore it is not clear that energy-adjustment could fully address underreporting given the fact that this error in particular is differential.(47, 48) Further research should assess the role of energy-adjustment in addressing underreporting.

Underreporting bias in dietary interviews varies with the type of dietary recall method used. A study comparing results from two 24-hour recall interviews to doubly labeled water found that Goldberg's cutoff method had a sensitivity of 50%, a specificity of 99% and a positive predictive value of 92% assuming a PAL of 1.55.(49) This suggests that Goldberg's cutoff correctly identifies the AR but misclassifies a high percentage of UR. These validity measures depend on the Goldberg cutoff which varies with the selected PAL. Sensitivity can be improved by assigning a higher overall PAL or specific PAL values based on physical activity measurements, but this will increase the cutoff and classify more individuals as UR. We used a PAL of 1.65 and three 24-hour recall interviews, which likely improves the sensitivity of the Goldberg method. Despite the low sensitivity, underreporting bias remains important, and, to date, most of the current nutrition literature fails to account for this bias.

Our study has some potential limitations. First, there is controversy regarding the 24-hour dietary recall as some believe it results in higher proportions of UR, compared to more thorough dietary assessment methods such as the diet record method(50) however some evidence shows that underreporting does not differ from one dietary assessment method to another.(1) Nevertheless, our study used repeated 24 h recalls on three non-consecutive days, which remains more precise than most dietary assessment methods. Second, dietary misreporting tends to vary with cultural differences, thus, our results may not be representative of populations that differ significantly to our target population. Third, in our main calculation of the Goldberg's cutoff, we did not use individual PAL and chose a more conservative cutoff because approximately 15% of our accelerometry data was missing. In addition, while the use of individual PAL is more precise, it would have resulted in over 50% of participants being classified as UR and increased the risk of falsely classifying participants as UR. Nevertheless, other studies have also used conservative cutoffs in children to identify underreporting.(9, 11) In addition, in our comparison of different adjustment approaches, the results obtained using PAL-specific cutoffs were similar to those obtained using the cutoff of 1.11. Authors should consider conducting sensitivity analyses with varying cutoffs to examine the precision of the cutoff selected and the robustness of their results.

In conclusion, UR in the QUALITY cohort tended to be generally unhealthy, with higher BMI, worse cardiometabolic risk factors and lower PAL compared to AR. It is of great importance to identify UR and address the bias that they introduce in study results, particularly when studying a cohort that is at a higher risk for obesity and with a high proportion of obese individuals as this may increase the proportion of UR. Failing to account for underreporting will likely result in spurious associations and incorrect interpretation of results.

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study, performed the data analysis, interpreted the results and drafted the manuscript. AB, MH, KGD and GP contributed to the design, and reviewed and edited the manuscript. KS and GP have primary responsibility for final content. All authors have read and approved the final version of the manuscript.

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Table 6.1. Comparison of population characteristics between underreporters and adequate reporters among boys and girls ages 8 to 10 from Quebec as part of the QUALITY cohort[1]

Characteristics	Underreporters (*n*=175)	Adequate reporters (*n*=438)	*P*
Age	9.9 ± 0.9	9.5 ± 0.9	<0.001
Male, %	49.0	57.0	0.07
BMI category, %			<0.001
Underweight (z-score < -2)	0	0.2	
Normal weight (z-score ≥ -2 & <1)	25.1	69.6	
Overweight (z-score ≥ 1 & < 2)	37.7	26.9	
Obese (z=score ≥ 2)	37.1	3.2	
Tanner stage, %			<0.001
Prepubertal	66.7	83.8	
Pubertal	33.3	16.2	
% fat mass	36.8 (27.8 to 42.8)	21.9 (15.6 to 30.1)	<0.001
Screen time (h/d)	2.6 (1.4 to 4.3)	2.1 (1.3 to 3.4)	0.006
SBP (mmHg)	95.7 (91.0 to 102.7)	92.7 (87.7 to 98.3)	<0.001
DBP (mmHg)	50.7 (46.3 to 53.7)	47.7 (44.7 to 51.0)	<0.001
Triglycerides (mmol/L)[2]	0.9 (0.6 to 1.2)	0.7 (0.5 to 0.9)	<0.001
HDL cholesterol (mmol/L)[2]	1.1 (0.9 to 1.2)	1.2 (1.0 to 1.4)	<0.001
LDL cholesterol (mmol/L)[2]	2.5 (2.1 to 2.8)	2.3 (1.9 to 2.6)	0.003
Parent education, %			0.11
no parent with high school diploma	1.7	0.9	
1 or 2 parents with high school diploma	8.1	5.3	
1 or 2 parents with community college or equivalent	41.9	36.8	
1 or 2 parents with university degree	48.3	57.1	
Family income (CAD)	38,972 ± 18,056	43,907 ± 18,404	0.003
Physical activity (CPM)[3]	519.4 (439.6 to 640.2)	580.3 (464.2 to 691.8)	0.005

[1] Values are means ± SDs or medians (IQRs), significantly different if $P<0.05$.
Abbreviations: body mass index: BMI, Canadian dollar: CAD; counts per minute: CPM; diastolic blood pressure: DBP; high-density lipoprotein cholesterol: HDL; interquartile range: IQR; low-density lipoprotein cholesterol: LDL; systolic blood pressure: SBP; standard deviation: SD.
[2] All analytes were measured in plasma
[3] Accelerometry data only completed for n=535 at baseline

Table 6.2. Comparison of dietary characteristics between underreporters and adequate reporters among children ages 8 to 10 from Quebec as part of the QUALITY cohort[1]

Dietary characteristics	Underreporters (*n*=175)	Adequate reporters (*n*=438)	*P*
Macronutrients			
Carbohydrates (g/d)	179.3 ± 38.6	239.8 ± 53.4	<0.001
Protein (g/d)	56.0 ± 16.5	72.2 ± 17.8	<0.001
Total fat (g/d)	47.2 ± 14.3	66.6 ± 17.2	<0.001
Saturated fat (g/d)	16.4 ± 5.7	23.9 ± 7.1	<0.001
Total energy intake (kcal/d)	1348 ± 276	1822 ± 351	<0.001
Boys	1405 ± 303	1901 ± 356	<0.001
Girls	1294 ± 237	1719 ± 316	<0.001
Energy-adjusted macronutrients			
Carbohydrate intake (% energy)	53.5 ± 6.7	52.7 ± 6.2	0.15
Protein intake (% energy)	16.7 ± 3.9	15.9 ± 3.1	0.012
Fat intake (% energy)	31.2 ± 5.1	32.8 ± 4.7	0.004
Saturated fat intake (% energy)	10.8 ± 0.2	11.8 ± 0.1	<0.001
Energy-adjusted micronutrients			
Calcium (mg/1000 kcal)	484.2 ± 134.4	515.8 ± 155.0	0.018
Iron (mg/1000 kcal)	7.1 ± 1.3	6.9 ± 1.7	0.22
Zinc (mg/1000 kcal)	5.2 ± 1.4	5.2 ± 1.7	0.99
Sodium (mg/1000 kcal)	1524 ± 352	1430 ± 319	0.001
Vitamin C (mg/1000 kcal)	81.0 ± 62.8	79.5 ± 51.9	0.77
Thiamin (mg/1000 kcal)	1.0 ± 0.3	1.0 ± 0.9	0.99
Riboflavin (mg/1000 kcal)	1.1 ± 0.3	1.2 ± 0.4	0.13
Niacin (NE/1000 kcal)	19.4 ± 5.4	18.1 ± 5.0	0.005
Vitamin A (RAE/1000 kcal)	405.5 ± 226.2	400.6 ± 195.1	0.79
Vitamin D (mcg/1000 kcal)	2.9 ± 1.9	3.5 ± 2.2	0.002
Folate (DFE/1000 kcal)	226.6 ± 78.1	218.1 ± 84.4	0.25
Food groups			
Fruits and vegetables (# of servings/d)	3.7 ± 2.0	4.6 ± 2.1	<0.001
Grain products (# of servings/d)	4.1 ± 1.5	4.9 ± 1.7	<0.001
Milk and dairy (# of servings/d)	1.4 ± 0.7	2.1 ± 1.0	<0.001
Meat and alternatives (# of servings/d)	1.6 ± 0.8	2.0 ± 0.9	<0.001
Sugar-sweetened beverages (ml/1000 kcal)	91.5 ± 109.4	63.8 ± 73.8	0.003
Number of snacks/day	4.5 ± 2.2	4.9 ± 2.1	0.025
Fiber (g/1000 kcal)	8.4 ± 2.3	7.8 ± 2.0	0.002

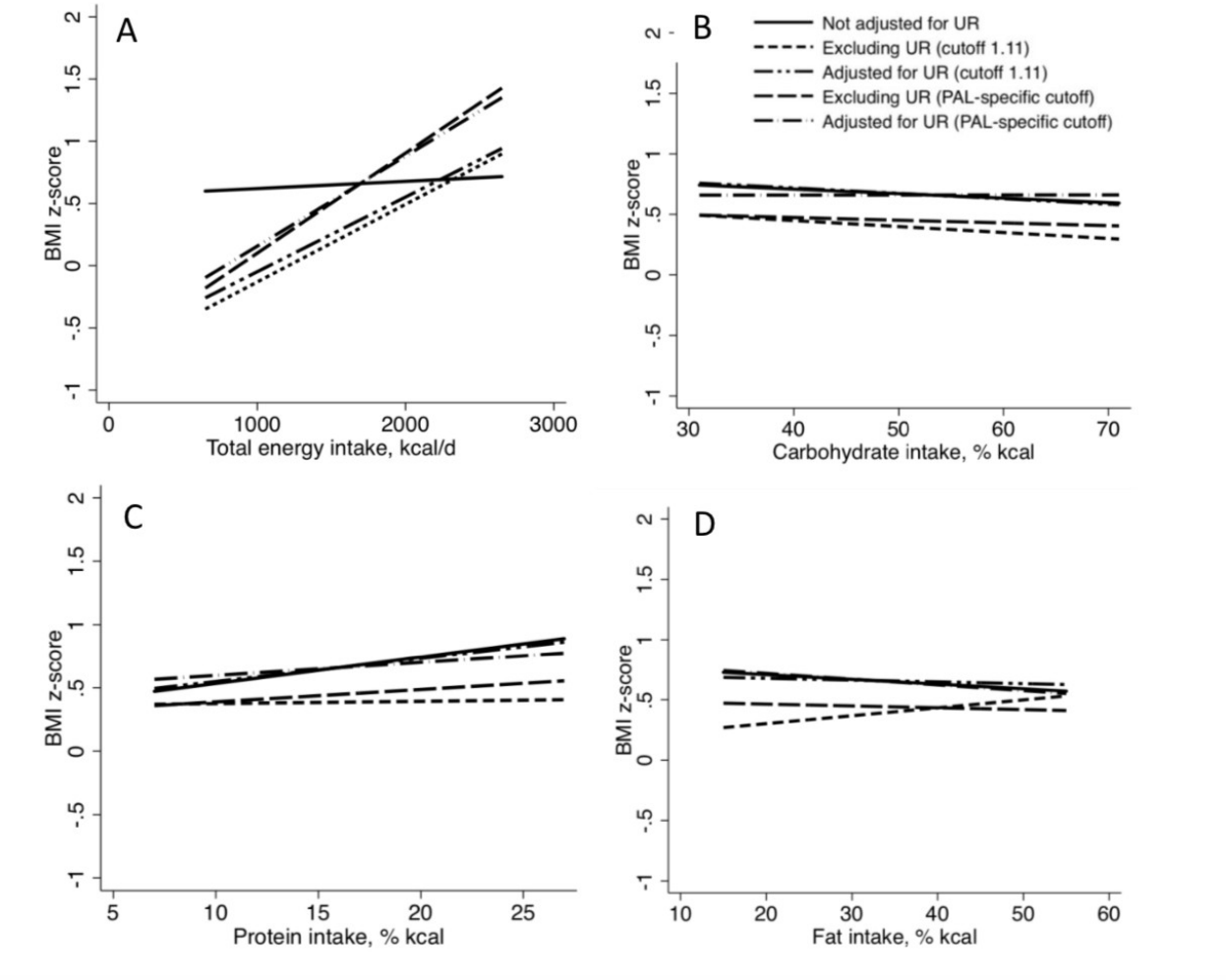
[1]Values are means ± SDs, significantly different if $P<0.05$.
Abbreviations: mean dietary folate equivalent: DFE; Niacin equivalent: NE; mean retinol activity equivalent: RAE; standard deviation: SD.

Table 6.3. Children and parental characteristics that predict underreporting in children of ages 8 to 10 in Quebec as part of the QUALITY study

	n	Crude OR (95% CI)	Adjusted[1] (n=563) OR (95% CI)
BMI z-score	613	3.48 (2.73 to 4.44)	3.07 (2.38 to 3.97)
Age (years)	613	1.52 (1.25 to 1.85)	1.46 (1.14 to 1.87)
Percent fat mass (%)[2]	608	1.12 (1.10 to 1.15)	-
Tanner (prepubertal vs. pubertal)	612	2.58 (1.72 to 3.87)	1.65 (0.99 to 2.73)
Family income (per $10,000)	608	0.86 (0.78 to 0.95)	0.92 (0.82 to 1.04)
Father's BMI	606	1.06 (1.02 to 1.09)	1.02 (0.98 to 1.06)
Mother's BMI	611	1.07 (1.04 to 1.10)	1.03 (1.00 to 1.07)

Values represent the odds (OR) and 95% confidence interval (95% CI) of being an underreporter (characterized as EI:BMR<1.11)
Abbreviations: body mass index: BMI; confidence interval: CI; odds ratio: OR.
Variables tested but not found statistically significant: sex, screen time, parent education, physical activity
[1]Adjusted model includes all variables except percent fat mass
[2]Percent fat mass was excluded from the fully adjusted model because of multicollinearity with BMI z-score

Figure 6.1. Association between energy and macronutrient consumption (A: total energy intake; B: carbohydrate density; C: protein density; D: fat density) at baseline and BMI z-score after 2 years in 8-10 year old children part of the QUALITY cohort comparing results with no adjustment to results with exclusion of underreporters and results with statistical adjustment for underreporters using a Goldberg's cutoff of 1.11 for all participants and individual PAL specific cutoff (all participants *n*=552, adequate reporters *n*=403)



Abbreviations: PAL physical activity level; UR underreporters.
All models are adjusted for tanner stage, family income, parent education, moderate to vigorous physical activity (counts per minute), mother's BMI and father's BMI

Postscript to Manuscript 1

This manuscript improves our understanding of the extent of misreporting in the QUALITY cohort and the potential impact of misreporting within this study. We showed that misreporters were predominantly underreporters, and they were more obese and had worse cardiometabolic risk factors. In addition, we showed that diet-disease association results tend to be biased toward the null due to underreporting. We also discussed strategies to address underreporting bias, including exclusion and statistical adjustment. With this study, we were able to decide on a strategy to address underreporting in the subsequent manuscripts of this thesis.

Using the results from manuscript 1, we can now apply this knowledge to the following 3 manuscripts. Specifically, we will opt against the exclusion of underreporters in order to avoid the introduction of selection bias. For analyses in manuscript 2, 3 and 4, we will use the continuous ratio of energy intake to basal metabolic rate (EI:BMR) to better match the distribution of the continuous exposure variables that we are aiming to correct. In manuscript 3, certain analyses will involve binary dietary exposures, for which we will use the binary underreporting variable with the cutoff of 1.11 calculated in manuscript 1.

CHAPTER 7: Dietary glycemic index and load and cardiovascular risk factors

Studies examining the associations between glycemic index and load on cardiovascular risk factors in children are scarce and most available studies are methodologically flawed. Understanding the impact of dietary glycemic index and load on cardiovascular risk factors in children is essential to develop adequate dietary recommendations for obesity and cardiovascular disease risk reduction. Therefore, in the following manuscript, our objectives were to assess the association between average dietary glycemic index and load on adiposity, blood lipids and blood pressure in school-aged children after 2 years.

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MANUSCRIPT 2

Original research article

Effects of dietary glycemic index and load on children's cardiovascular risk factors

Running head: Glycemic load and cardiovascular risk factors

Karine Suissa[1], Andrea Benedetti[1,2,3], Mélanie Henderson[4,5], Katherine Gray-Donald[6], Gilles Paradis[1]

Affiliations:

[1]Department of Epidemiology, Biostatistics, and Occupational Health, McGill University, Montreal, Quebec, Canada

[2]Department of Medicine, McGill University, Montreal, Quebec, Canada

[3]Respiratory Epidemiology and Clinical Research Unit, McGill University Health Centre, Montreal, Quebec, Canada

[4]Research Center of Centre Hospitalier Universitaire Sainte-Justine, Montreal, Canada.

[5]Department of Pediatrics, Faculty of Medicine, Université de Montréal, Montreal, Canada.

[6] School of Dietetics and Human Nutrition, McGill University, Montreal, Quebec, Canada (retired)

Word Count: 3,000

Address for Correspondence:

Gilles Paradis, MD, MSc, FRCPC
Professor and Chair
Department of Epidemiology, Biostatistics and Occupational Health
McGill University - Purvis Hall
1020 Pine Avenue West
Montreal, Quebec, Canada, H3A 1A2
Tel.: 514-398-6259
Fax: 514-398-2373
Email: chair.epid@mcgill.ca

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List of abbreviations:
CV: cardiovascular
TG: triglycerides
HDL: high-density lipoprotein
CVD: cardiovascular diseases
GI: glycemic index
GL: glycemic load
QUALITY: QUébec Adipose and Lifestyle InvesTigation in Youth
BMR: basal metabolic rate
BMI: body mass index
BMIz: BMI z-score
SBP: systolic blood pressure
DBP: diastolic blood pressure
LDL: low-density lipoprotein
SD: standard deviation
IQR: interquartile range

ABSTRACT

Purpose: Consumption of foods high in glycemic index (GI) and glycemic load (GL) are associated with cardiovascular (CV) diseases in adulthood. We examined whether GI and GL predict CV risk factors in children after 2 years of follow-up.
Methods: The QUALITY study recruited children aged 8-10 years. Three 24-hour recalls were administered at baseline and individual average daily GI and GL scores were calculated. CV risk factors included body mass index z-score (BMIz), percent fat mass (DEXA), triglycerides, LDL and HDL cholesterol, and systolic and diastolic blood pressure. We used multiple imputation for missing data. Main analyses consisted of multiple linear regression adjusted for anthropometric, socio-economic and dietary factors. We evaluated mediation by BMIz.
Results: After two-years, the highest dietary GL tertile compared to the lowest was associated with increased BMIz (mean difference (MD)=1.1, 95%CI=0.88,1.31), fat mass (MD=10.8%, 95%CI= 8.62,13.0), triglycerides (MD=0.17 mmol/L, 95%CI=0.07,0.28), and decreased HDL (MD=-0.13 mmol/L, 95%CI= -0.19,-0.07) but not LDL or blood pressure. The GL-TG and the GL-HDL associations were mediated by BMIz.
Conclusion: GL predicts increased BMIz, percent fat mass and triglycerides, and decreased HDL in young children after 2 years. Recommendations to decrease CV risk in children should include lowering foods high in GL.

Keywords: glycemic index, glycemic load, cardiovascular risk factors, school-aged children

INTRODUCTION

Between 2004 and 2013, the combined overweight and obesity prevalence in 2-17 year-old Canadians decreased but remained high at 31.4%. [1] In the United States, the prevalence of obesity in 2016 was 19.1 and 17.8% in boys and girls respectively. [2] Childhood obesity has short-term metabolic and cardiovascular (CV) effects, including increased fasting insulin and triglycerides (TG), lowered high-density lipoprotein (HDL) cholesterol and increased blood pressure. It has been associated with the development of type 2 diabetes, and hypertension in children and adolescents, and may lead to cardiovascular diseases (CVD) later in life. [3,4] Among a number of risk factors, dietary intake has an important influence on obesity and CVD risk factors. Particularly, refined carbohydrates tend to be absorbed faster into the bloodstream causing excessive insulin secretion and resulting in increased hepatic and cellular fat storage. Excess energy intake, specifically in the form of refined carbohydrates, can lead to obesity, worsened blood lipid profiles and ultimately to CVD. [6-8]

The glycemic index (GI) is a measure of blood glycemic response resulting from various qualities of dietary carbohydrates (by definition, a high quality [low GI] carbohydrate does not raise blood glucose as much as a low quality [high GI] carbohydrate, relative to an equal weight of glucose), whereas glycemic load (GL) is an indicator of both quality (GI) and quantity of carbohydrates consumed. [9] GI and GL have been positively linked to adiposity, dyslipidemia and CVD in adults, [10-14] however few observational studies have assessed this association in youth, and reported findings have been inconsistent, likely owing to methodological flaws, including dietary measurement error and differential recall, and varying populations by ethnic and cultural background. [15-19]

In this study, we used data from the ongoing QUébec Adipose and Lifestyle InvesTigation in Youth (QUALITY) study, a cohort of children from Quebec, Canada, aged 8-10 years at baseline and with at least one obese parent, to identify whether dietary GI and GL affect CV risk factors. Specifically, the main objective was to examine how dietary GI and GL at baseline predict adiposity, lipid profiles and blood pressure, two years later. Identifying longitudinal associations between GI and GL, scores that are easily understandable, and cardiovascular risk

factors could add to current knowledge on pediatric obesity and CVD prevention and help improve nutritional counselling by dietitians and physicians and potentially also help families make healthy food choices.

METHODS

Study population

The design and methods of the QUALITY study has been previously described. [20] A total of 630 children aged 8-10 years and both biological parents were recruited and, two years later, the follow-up included 564 children (89.5% retention). The QUALITY cohort used a school-based sampling strategy to identify potential participants. Caucasian children of Western European ancestry aged 8–10 years with at least one obese biological parent (body mass index (BMI) ≥30 kg/m$_2$ or waist circumference ≥102 cm (men) and ≥88 cm (women)) were included. The cohort was restricted to Caucasian families to reduce genetic admixture. Families were excluded if the mother was pregnant or breastfeeding, or if the family had plans to move out of province. Children that had any of the following criteria were excluded: (i) type 1 or type 2 diabetes; (ii) a serious illness, psychological condition or cognitive disorder; (iii) treatment with oral anti-hypertensive medication or steroids; and (iv) following a very restricted diet (<600kcal/day).

Measurements

Trained dietitians administered three unannounced non-consecutive 24-hour dietary recalls including one weekend day over the telephone within 8-12 weeks following the baseline visit. A disposable kit of food portion models (for example, a graduated cup, a bowl, etc.) was provided to participants at the baseline visit, in conjunction with a training and practice session for children and parents. Interviews were conducted with the child, and parents helped with food descriptions and cooking details. The dietary data collected from 613 participants were entered in the CANDAT Nutrient Analysis Software (Godin and associates, London, Ontario, 2007), which calculates nutrient composition of foods based on the Canadian Nutrition Files. Underreporters of energy intake were identified using the Goldberg equation[21].

The steps for assigning GI and GL to foods in the database were as follows. First, we assigned a value of zero to each food group containing less than or equal to 5 grams of carbohydrate per 100 grams.[22] Next, if a food was listed in the International table of GI,[23] we used the corresponding GI score. Foods without a preassigned GI value in the International table of GI [23] were assigned a GI based on the closest nutritionally matching food. [22,24] Finally, we multiplied every GI value by the available carbohydrate content in each food to obtain a GL score. We obtained an average daily GI and GL for each participant by calculating the sum of the scores by recall day and then averaging the totals of the 3 dietary recalls.

Anthropometric measurements were collected according to a standardized protocol with participants dressed in light indoor clothing with no shoes, using a stadiometer for height (nearest 0.1 cm), and an electronic scale for weight (nearest 0.1 kg). Height and weight were measured twice, and a third measure was obtained if the first two measures differed by 0.2 centimeters or 0.2 kilograms or more. The final value was the average of the two closest measurements. BMI was calculated as weight in kilograms divided by height in meters squared. Age- and sex-specific BMI z-score (BMIz) was obtained using CDC growth charts[25] Percent body fat was assessed using dual energy X-ray absorptiometry (DEXA, Prodigy Bone Densitometer System, DF-14664, GE Lunar Corporation, Madison, WI, USA). At each clinic visit, blood was collected from both children and parents by venipuncture following an overnight fast. Blood samples were centrifuged, aliquoted and stored at minus 80 Celsius and were analyzed at the Department of Biochemistry at Centre Hospitalier Universitaire Sainte-Justine.[20] Triglycerides and HDL-cholesterol concentrations were determined on a Synchron LX®20 with Beckman Instruments reagents and expressed as mmol/L. Low-density lipoprotein (LDL) cholesterol was calculated using the Friedewald equation.[26]

Blood pressure was measured on the right arm with participants in seated position, using an oscillometric instrument (Dinamap XL, model CR9340, Critikon Company, FL, USA). Five readings were recorded and the mean value of the last three readings was used for Systolic Blood Pressure (SBP) and Diastolic Blood Pressure (DBP). Age, sex and height specific z-scores were calculated following the Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents.[27]

Physical activity was assessed over a 7-day period using an Actigraph LS 7164 activity monitor (Actigraph LLC, Pensacola, Florida). Accelerometry data were downloaded as 1-min epochs and were processed using standardized quality control and data reduction procedures.[28] Participants were retained if they had at least four days with a minimum of 10 hours of wear time.[29] For our analyses, we used daily step counts to adjust for physical activity. Screen time was assessed by interviewer-administered questionnaire that collected daily hours of television, computer or video game use. Data on parental education and household income were collected from questionnaires. Sexual maturity was observed by trained nurses and scored according to the Tanner stages.[30,31] For our analyses, we categorized children into prepubertal (stage 1) or pubertal (stages 2 and higher).

Exposure and outcome definition

The outcomes of interest included BMIz, percent fat mass, blood lipids including TG, HDL and LDL cholesterol and SBP z-score and DBP z-score after a 2-year follow-up. Independent variables were baseline GI and GL.

Statistical analyses

Descriptive statistics are reported as mean (standard deviation (SD)) or median (interquartile range (IQR)) for both baseline and follow-up visits. We used multiple imputation (Proc MI in SAS 9.3) to account for missing data of covariates, particularly the physical activity variable that had 15 percent missing data. All dietary variables were adjusted for energy intake using the residual method.[32] We estimated multiple linear regression models for each outcome of interest, with baseline GI or GL (residuals) as independent variables, adjusted for important confounders measured at baseline (age, sex, pubertal vs. prepubertal, physical activity, family income, parental education, fat and protein intake (residuals), season, and underreporting (ratio of energy intake and estimated energy requirement)). Age and sex were not included in the BMIz, SBP z-score and DBP z-score models because these outcome measures are already adjusted for age and sex. We assessed linearity with adjusted linear regression splines of predicted BMIz, percent fat mass, TG, LDL, HDL, SBP z-score and DBP z-score as a function of GL which showed

nearly linear relationships between GL and outcomes of interest, therefore estimates of linear regressions are presented. We tested for interactions between each exposure variables (GI and GL) and sex and with BMI category (under/normal weight vs. overweight/obese) by introducing an interaction term one at a time in adjusted models. As a secondary analysis, we assessed mediation by BMIz at baseline, assuming diet recall was an indicator of usual intake, using the Baron and Kenny approach.[33] While we chose to adjust for underreporting as a continuous variable to reduce residual confounding, we also conducted additional analyses using a binary parametrization to facilitate comparisons with some authors who used the categorized underreporting variable for adjustment. We used SAS version 9.3 for analyses and STATA version 13.1 for graphics.

RESULTS

Among the 630 participants recruited at baseline, 66 were lost to follow-up. There were no significant differences between those included and those lost to follow-up in the analyses presented herein with respect to age, BMIz and sex. Population characteristics at baseline and follow-up are shown in table 1. After two years, children had a higher percent fat mass, spent approximately one additional hour of screen time per day and were less physically active (Table 7.1).

In multiple linear regression, GI at baseline did not predict any cardiometabolic risk factors after 2 years (Table 7.2). GL predicted BMIz (ß=0.03, 95%CI=0.02,0.03), percent fat mass (ß=0.29, 95%CI=0.25,0.33), TG (ß=0.005, 95% CI=0.003,0.007), and HDL cholesterol (ß=-0.003, 95%CI=-0.004,-0.002) after 2 years per 10 units of GL, but not LDL cholesterol, SBP z-score and DBP z-score (Table 7.3). When exposure was analyzed as tertiles, highest dietary GL tertile compared to the lowest was associated with an increased BMIz (mean difference=1.1, 95%CI=0.88,1.31), percent fat mass (mean difference=10.8, 95%CI=8.62,13.0), triglycerides (mean difference=0.17, 95%CI=0.07,0.28), and decreased HDL (mean difference=-0.13, 95%CI=-0.19,-0.07). No statistically significant interactions were found with BMI category or sex.

Mediation analysis showed total effects of baseline GL on TG and HDL after 2 years that were attenuated when BMIz was included in the model to evaluate the direct effect (TG: ß=0.003,

95%CI (0.001,0.007); HDL: ß=-0.001, 95%CI (-0.003,0.001)) indicating that BMIz mediated the association between GL and TG and GL and HDL (Figures 7.1-7.2).

Our sensitivity analyses revealed similar results to our main analysis of GI and GL (Tables 7.S1-7.S2).

DISCUSSION

Cardiovascular risk factors tend to track over time, with research supporting the idea that worse cardiometabolic risk profiles in childhood will result in deleterious cardiometabolic profiles in adulthood.[34] The American Academy of Pediatrics recommends prevention of CVD by maintaining healthy weight and blood lipid levels in childhood.[35] Our study revealed an association between high dietary GL and overall worse cardiometabolic profiles 2 years later in children at risk for obesity.

Specifically, GL but not GI predicted increased adiposity and unhealthy blood lipids in our population of 8 to 10-year-old children after 2 years. In addition, the association between GL and blood lipids was mediated by BMIz, indicating that the association is mainly explained by BMI. We did not observe any associations with GI, carbohydrate quality, but did observe associations with GL, carbohydrate quality and quantity, implying that it is important to consider both quality and quantity of carbohydrates, rather than quality alone when selecting dietary carbohydrates.

GL may exert harmful effects via several pathways. The consumption of high GI foods induces immediate hyperglycemia due to the quick uptake of glucose in the blood stream.[36,37] This provokes a hyperinsulinemic response to restore normal blood glucose levels, resulting in a relative hypoglycemic state.[36,37] This insulin-induced relative hypoglycemic state may provoke prolonged hyperphagia, over-eating, even after normal blood glucose levels have been restored.[36,37] Moreover, the hyperinsulinemia state leads to a preferential behavioral selection of high GL foods, creating a cycle of hypoglycemia and hyperphagia resulting in weight gain and obesity.[36-39] Following a high GL meal, a counterregulatory hormonal response is triggered to restore normal glucose levels. This response stimulates processes that elevate free fatty acid concentrations to

levels higher than observed with a low GL diet.[40,41] In turn, increased lipid accumulation in adipose tissues leads to weight gain, increased inflammation and decreased vasodilation, factors known to worsen CVD risk factors.[42,43]

We observed increasing BMIz and percent fat mass in children with increasing GL, but not GI. In fact, after two years, those that consumed a dietary GL in the highest tertile were more than one full BMIz higher and had 10% greater percent fat mass compared to children in the lowest tertile of dietary GL. Nine previous studies, including only two other longitudinal studies, have examined the association between GI and GL and adiposity in children and have reported inconsistent results. Analyses from the Dortmund Nutrition and Anthropometric Longitudinally Designed Study cohort found no association between change in GI and GL and concurrent changes in BMIz and percent body fat.[18] Consistent with our results, a longitudinal study in 2,353 Australian 12 year-olds[15] showed no association between GI and change in adiposity, but observed a 0.77 kg/m$_2$ increase in BMI for every 50.89 unit (1 SD) increase in dietary GL in girls. In our study population, we did not observe differences between sexes. This discrepancy may be due to age and cultural differences between the Australian cohort and the QUALITY cohort. The remaining 7 studies were cross-sectional. Two cross-sectional studies found a positive association between GI but not GL and adiposity in children,[44,45] and one study found associations with both GI and GL.[46] The other four studies found no associations.[17-19,47] In addition to inherent methodological limitations of cross-sectional studies such as reverse causation, the studies mentioned above also had other methodological problems, including confounding caused by underreporting,[15,19,46] measurement error mainly resulting from an insufficient number of nutritional recalls,[46] and selection bias due to selective inclusion criteria and high rates of non-response.[15,44,47] Furthermore, the divergent results may be explained by differences in study populations which varied by age, ethnic origins and dietary culture of children.

Our results also showed an association between high dietary GL, but not GI, with worsened blood lipids after 2 years, specifically higher TG and lower HDL. Physiologically, elevated insulin levels lead to increased hepatic fat synthesis. This results in an accumulation of TG and cholesterol esters in the blood.[48] Population studies in adults have reported indirect associations between high GI and GL diets and high insulin secretion resulting in increased TG[10,49,50] and LDL cholesterol[49]

and decreased HDL cholesterol. [10,50,51] However, only two cross-sectional studies have examined the association between GI and GL and lipid profiles of children and reported inconsistent results.[52,53] In addition, the association between dietary GL and blood lipids was mediated by BMIz, however, there was evidence of a possible direct effect of dietary GL on TG by pathways that do not include BMIz. The mediating role of adiposity should be further examined in other observational studies with various indicators of adiposity.

Our study is one of the few studies to assess the longitudinal association of GI and GL on cardiovascular risk factors in children and the first to examine mediation by BMI. In addition, the QUALITY cohort data was rigorously collected using the most recent measurement tools and provides a large number of covariates.

Our study has potential limitations. First, the QUALITY study had some losses to follow-up. However, since only 10 percent of children were lost to follow-up, our results should not have been significantly altered. Second, while the 24h recall is a strong measurement tool for dietary intake, especially when conducted on three or more non-consecutive days, it can result in measurement error because it relies on memory and recall. However, the use of disposable containers and rulers to help with portion estimations and the involvement of the parents at each interview should reduce recall bias. As well, the fact that interviews were unannounced should considerably reduce reporting bias. In addition, to account for differential reporting, we adjusted for underreporting. When foods consumed at school were obtained from the school cafeteria, parents did not observe their child's dietary intake at school and could not have participated in the recall for that meal. However, findings from several studies have shown that by the age of 8-10 years children are capable of reporting their food intake during a 24-hour recall as reliably as with the help of their parents, particularly on regular weekdays. [54-56] As well, while random error can result from intra-individual variation in intake from day to day, since the interviews were repeated on three non-consecutive days and averaged across those days, random error should be reduced. Third, although we adjusted for a variety of dietary and non-dietary confounders, there is still a potential for residual confounding by variables strongly correlated with dietary GI or GL that may also explain or mask an association. Fourth, because we only had two timepoints available, we had to use baseline BMIz as the mediator for our mediation analysis. We had to assume that the 3 non-

consecutive 24-hour recalls represent short-term usual/habitual dietary intake. In addition, we had to remain cautious in our causal interpretation of the results of the mediation analysis because the causal inference assumptions of consistency, exchangeability and positivity may not be met. [57] Finally, our results are principally generalizable to Caucasian children at risk of obesity. Further research examining these associations among children of different ethnic backgrounds would be informative.

CONCLUSION

In our longitudinal cohort of children initially aged 8-10, GL, but not GI, predicted 2-year increases in BMI, fat mass and TG and decreases in HDL cholesterol. Our results highlight the important role of GL, specifically carbohydrate quality and quantity, in cardiovascular risk factors in children. Dietary recommendations for children in the prevention of obesity and CVD should focus on lowering GL.

CONTRIBUTIONS

KS designed the research question for this project, conducted the analysis, interpreted results and wrote the manuscript. AB, MH, KGD and GP participated in the research question design (defining outcomes, identifying confounders, determining appropriate analysis methods), reviewed and edited the manuscript.

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Table 7.1. Population characteristics of children in the QUALITY cohort at baseline and first follow up visit

Characteristic	Baseline n=630	Follow-up n=564
Age (years), mean (SD)	9.6 (0.9)	11.7 (0.9)
Male, %	54.4	55.5
BMI category, %		
Underweight (z-score < -2)	0.3	0.9
Normal weight (z-score ≥ -2 & <1)	56.7	58.3
Overweight (z-score ≥ 1 & < 2)	30.0	28.4
Obese (z-score ≥ 2)	13.0	12.4
Tanner stage, %		
Prepubertal	78.4	33.2
Pubertal	21.6	66.8
Percent fat mass, median (IQR)	25.3 (17.4 to 35.2)	27.8 (19.4 to 36.4)
Screen time, median (IQR), h/d	2.2 (1.3 to 3.7)	2.9 (1.9 to 4.4)
SBP z-score, median (IQR)	-0.79 (-1.26 to -0.35)	-0.85 (-1.37 to -0.39)
DBP z-score, median (IQR)	-1.09 (-1.40 to -0.83)	-1.09 (-1.39 to -0.80)
Triglycerides, median (IQR)	0.7 (0.6 to 1.0)	0.7 (0.5 to 0.9)
HDL cholesterol, median (IQR)	1.2 (1.0 to 1.3)	1.1 (1.0 to 1.3)
LDL cholesterol, median (IQR)	2.3 (2.0 to 2.7)	2.2 (1.9 to 2.6)
Parent education		
no parent with high school diploma	1.4	0.8
1 or 2 parents with high school diploma	6.4	6.4
1 or 2 parents with community college or equivalent	37.8	42.9
1 or 2 parents with university degree	54.4	49.9
Family income, mean (SD)	42,360 (18,574)	48,643 (22,191)
Glycemic index, mean (SD)	52.2 (4.2)	-
Glycemic load, mean (SD)	110.1 (30.8)	-
Carbohydrate intake, mean per day (SD), g	221.3 (56.0)	-
Energy intake, mean per day (SD), kcal	1681.8 (388.4)	-
Sugar-sweetened beverages, median (IQR), ml	67.9 (0.0 to 189.5)	-
Number of snacks, median (IQR)	5 (3 to 6)	-
Physical activity, median (IQR), counts per minute*	559.1 (459.0 to 675.1)	462.3 (374.5 to 587.3)

Abbreviations: SD standard deviation; IQR inter-quartile range

*Accelerometry data only completed for n=535 at baseline and n=418 at follow-up visit

Table 7.2. Longitudinal association between dietary glycemic index at baseline and cardiometabolic risk outcomes after 2 years of follow up in children from the QUALITY cohort, ages 8 to 10 at baseline

	Continuous GI†	Tertiles of Glycemic Index‡		
		1	2	3
Outcome				
BMI z-score				
Mean difference (95% CI)	0.11 (-0.08, 0.31)	0	-0.01 (-0.22, 0.19)	0.10 (-0.11, 0.30)
Adjusted mean difference (95% CI)*	-0.11 (-0.30, 0.08)	0	-0.14 (-0.34, 0.05)	-0.11 (-0.31, 0.08)
Fat mass (%)				
Mean difference (95% CI)	0.66 (-1.30, 2.61)	0	-0.86 (-2.92, 1.20)	0.38 (-1.64, 2.40)
Adjusted mean difference (95% CI)	-0.78 (-2.65, 1.10)	0	-1.43 (-3.34, 0.49)	-1.03 (-2.30, 0.90)
Triglycerides (mmol/L)				
Mean difference (95% CI)	0.05 (-0.03, 0.01)	0	-0.02 (-0.11, 0.06)	0.07 (-0.02, 0.15)
Adjusted mean difference (95% CI)	0.005 (-0.08, 0.09)	0	-0.05 (-0.13, 0.04)	0.02 (-0.07, 0.11)
LDL cholesterol (mmol/L)				
Mean difference (95% CI)	0.02 (-0.10, 0.14)	0	0.01 (-0.12, 0.13)	0.03 (-0.09, 0.15)
Adjusted mean difference (95% CI)	0.003 (-0.12, 0.13)	0	-0.01 (-0.14, 0.11)	0.02 (-0.11, 0.14)
HDL cholesterol (mmol/L)				
Mean difference (95% CI)	-0.04 (-0.09, 0.01)	0	-0.02 (-0.01, 0.03)	-0.03 (-0.08, 0.02)
Adjusted mean difference (95% CI)	-0.003 (-0.05, 0.05)	0	-0.002 (-0.05, 0.05)	0.003 (-0.05, 0.05)
SBP z-score				
Mean difference (95% CI)	0.08 (-0.07, 0.23)	0	0.06 (-0.09, 0.22)	0.07 (-0.08, 0.23)
Adjusted mean difference (95% CI)*	0.02 (-0.14, 0.17)	0	0.01 (-0.15, 0.17)	0.01 (-0.15, 0.17)
DBP z-score				
Mean difference (95% CI)	0.07 (-0.02, 0.16)	0	0.04 (-0.06, 0.13)	0.07 (-0.02, 0.17)
Adjusted mean difference (95% CI)*	0.03 (-0.06, 0.13)	0	0.02 (-0.08, 0.11)	0.03 (-0.07, 0.13)

Abbreviations: body mass index: BMI; confidence interval: CI; diastolic blood pressure: DBP; high-density lipoprotein: HDL; low-density lipoprotein: LDL; systolic blood pressure: SBP
All crude models were adjusted for underreporting (ratio of energy intake and estimated energy requirement). All multiple linear regression models were adjusted for pubertal vs non-pubertal status, screen time, physical activity (CPM), family income, parent education (4 categories), ratio of energy intake and estimated energy requirement, fat and protein intake (residuals), season
*Age and sex were not included in the BMI z-score, SBP z-score and DBP z-score models

Interpretation: †Continuous model: every 10 unit increase in GI at baseline is associated with a mean increase in outcome of x. ‡Tertile model: consuming a dietary GI in the highest tertile compared to the lowest reference tertile at baseline is associated with an increased outcome of x after 2 years of follow-up

Table 7.3. Longitudinal association between dietary glycemic load at baseline and cardiometabolic risk outcomes after 2 years of follow up in children from the QUALITY cohort, ages 8 to 10 years at baseline

	Continuous GL†	Tertiles of Glycemic Load‡		
		1	2	3
Outcome				
BMI z-score				
Mean difference (95% CI)	0.01 (0.001, 0.002)	0	0.10 (-0.11, 0.30)	0.54 (0.32, 0.75)
Adjusted mean difference (95% CI)*	0.03 (0.02, 0.03)	0	0.37 (0.19, 0.55)	1.10 (0.88, 1.31)
Fat mass (%)				
Mean difference (95% CI)	0.11 (0.07, 0.18)	0	1.34 (-0.69, 3.36)	4.78 (2.60, 6.70)
Adjusted mean difference (95% CI)	0.29 (0.25, 0.33)	0	4.12 (2.32, 5.93)	10.8 (8.62, 13.0)
Triglycerides (mmol/L)				
Mean difference (95% CI)	0.001 (-0.001, 0.003)	0	0.08 (-0.16, 0.01)	0.03 (-0.06, -0.13)
Adjusted mean difference (95% CI)	0.005 (0.003, 0.007)	0	-0.01 (-0.10, 0.08)	0.17 (0.07, 0.28)
LDL cholesterol (mmol/L)				
Mean difference (95% CI)	-0.0004 (-0.003, 0.002)	0	0.02 (-0.10, 0.15)	-0.03 (-0.17, 0.10)
Adjusted mean difference (95% CI)	0.002 (-0.001, 0.0001)	0	0.07 (-0.06, 0.20)	0.07 (-0.08, 0.23)
HDL cholesterol (mmol/L)				
Mean difference (95% CI)	-0.001 (-0.002, 0.0001)	0	0.02 (-0.03, 0.07)	-0.05 (-0.11, 0.004)
Adjusted mean difference (95% CI)	-0.003 (-0.004, -0.002)	0	-0.02 (-0.07, 0.03)	-0.13 (-0.19, -0.07)
SBP z-score				
Mean difference (95% CI)	0.001 (-0.002, 0.004)	0	-0.04 (-0.19, 0.12)	-0.01 (-0.18, 0.16)
Adjusted mean difference (95% CI)*	0.004 (0.000, 0.008)	0	0.02 (-0.14, 0.18)	0.07 (-0.12, 0.26)
DBP z-score				
Mean difference (95% CI)	0.0003 (-0.002, 0.002)	0	0.03 (-0.06, 0.13)	0.03 (-0.07, 0.14)
Adjusted mean difference (95% CI)*	-0.0001 (-0.002, 0.003)	0	0.04 (-0.06, 0.14)	0.03 (-0.09, 0.14)

Abbreviations: body mass index: BMI; confidence interval: CI; diastolic blood pressure: DBP; high-density lipoprotein: HDL; low-density lipoprotein: LDL; systolic blood pressure: SBP
All crude models were adjusted for underreporting (ratio of energy intake and estimated energy requirement). All multiple linear regression models were adjusted for age, sex, pubertal vs non-pubertal status, screen time, physical activity (CPM), family income, parent education (4 categories), ratio of energy intake and estimated energy requirement, energy (residual method), fat and protein intake (residuals), season

*Age and sex were only included in the percent fat mass, TG, LDL and HDL models
Interpretation: †Continuous model: every 10 unit increase in GL at baseline is associated with a mean increase in outcome of x. ‡Tertile model: consuming a dietary GL in the highest tertile compared to the lowest reference tertile at baseline is associated with an increased outcome of x after 2 years of follow-up

Figure 7.1. The total, direct and indirect effects of glycemic load on triglycerides considering adiposity (BMI z-score) as a mediator (β (95% CI)). Direct effects can be interpreted as follows: for every 10-unit increase in glycemic load, β can be interpreted as the unit change in triglycerides independent of BMI z-score

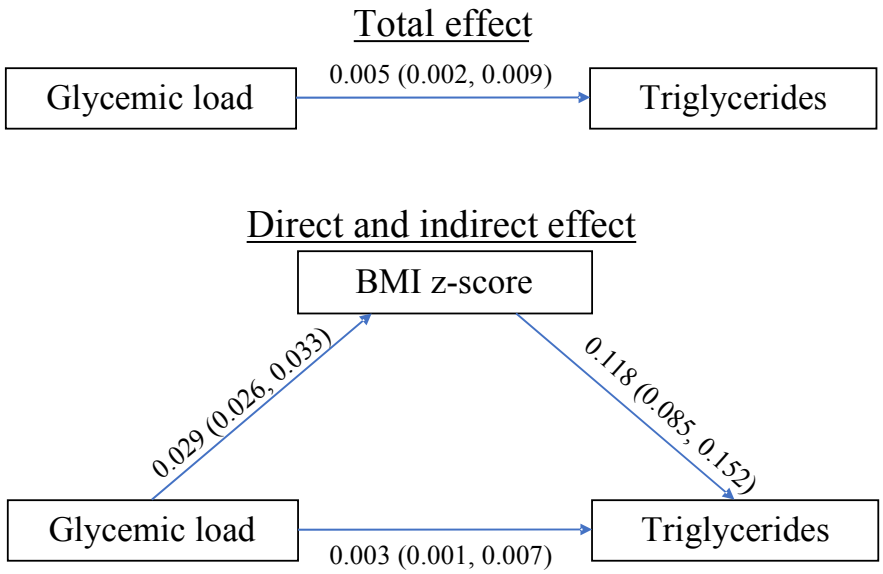
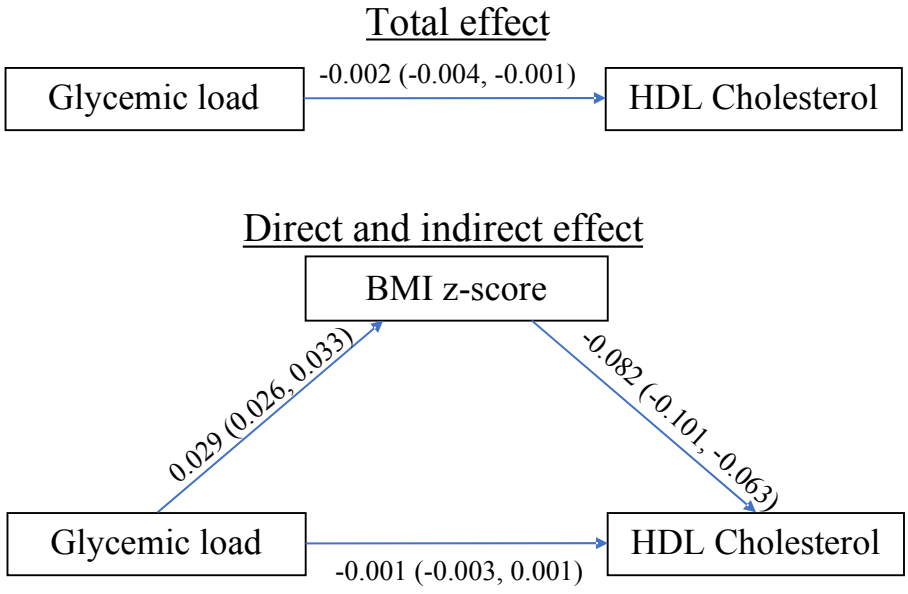


Figure 7.2. The total, direct and indirect effects of glycemic load on HDL cholesterol considering adiposity (BMI z-score) as a mediator (β (95% CI)). Direct effects can be interpreted as follows: for every 10-unit increase in glycemic load, β can be interpreted as the unit change in HDL cholesterol independent of BMI z-score



Supplemental material

Table 7.S1. Analysis using binary variable for underreporting in longitudinal association between dietary glycemic index at baseline and cardiometabolic risk outcomes after 2 years of follow up in children from the QUALITY cohort, ages 8 to 10 at baseline

	Continuous GI	Tertiles of Glycemic Index		
		1	2	3
Outcome				
BMI z-score				
Mean difference (95% CI)	0.08 (-0.11, 0.28)	0	-0.01 (-0.22, 0.19)	0.06 (-0.15, 0.26)
Adjusted mean difference (95% CI)*	-0.04 (-0.23, 0.16)	0	-0.07 (-0.27, 0.13)	-0.06 (-0.27, 0.13)
Fat mass (%)				
Mean difference (95% CI)	0.35 (-0.16, 0.23)	0	-0.82 (-2.79, 1.16)	-0.04 (-2.06, 1.99)
Adjusted mean difference (95% CI)	-0.13 (-0.21, 0.18)	0	-0.82 (-2.79, 1.40)	-0.60 (-2.60, 1.40)
Triglycerides (mmol/L)				
Mean difference (95% CI)	0.04 (-0.04, 0.13)	0	-0.02 (-0.11, 0.06)	0.06 (-0.03, 0.14)
Adjusted mean difference (95% CI)	0.01 (-0.07, 0.09)	0	-0.04 (-0.12, 0.05)	0.02 (-0.06, 0.11)
LDL cholesterol (mmol/L)				
Mean difference (95% CI)	0.02 (-0.10, 0.13)	0	0.002 (-0.12, 0.12)	0.02 (-0.10, 0.14)
Adjusted mean difference (95% CI)	0.001 (-0.12, 0.12)	0	-0.01 (-0.14, 0.11)	0.01 (-0.12, 0.14)
HDL cholesterol (mmol/L)				
Mean difference (95% CI)	-0.03 (-0.08, 0.02)	0	-0.03 (-0.08, 0.03)	-0.03 (-0.08, 0.02)
Adjusted mean difference (95% CI)	-0.01 (-0.06, 0.04)	0	-0.01 (-0.06, 0.04)	-0.004 (-0.05, 0.05)
SBP z-score				
Mean difference (95% CI)	0.08 (-0.08, 0.23)	0	0.07 (-0.09, 0.22)	0.07 (-0.09, 0.23)
Adjusted mean difference (95% CI)*	0.05 (-0.11, 0.21)	0	0.03 (-0.12, 0.19)	0.03 (-0.13, 0.19)
DBP z-score				
Mean difference (95% CI)	0.07 (-0.02, 0.16)	0	0.04 (-0.06, 0.13)	0.08 (-0.02, 0.17)
Adjusted mean difference (95% CI)*	0.04 (-0.06, 0.13)	0	0.02 (-0.07, 0.12)	0.04 (-0.06, 0.14)

Abbreviations: body mass index: BMI; confidence interval: CI; diastolic blood pressure: DBP; high-density lipoprotein: HDL; low-density lipoprotein: LDL; systolic blood pressure: SBP
All crude models were adjusted for underreporting (ratio of energy intake and estimated energy requirement). All multiple linear regression models were adjusted for pubertal vs non-pubertal status, screen time, physical activity (CPM), family income, parent education (4 categories), ratio of energy intake and estimated energy requirement, fat and protein intake (residuals), season
*Age and sex were not included in the BMI z-score, SBP z-score and DBP z-score models
Interpretation: †Continuous model: every 10 unit increase in GI at baseline is associated with a mean increase in outcome of x. ‡Tertile model: consuming a dietary GI in the highest tertile compared to the lowest reference tertile at baseline is associated with an increased outcome of x after 2 years of follow-up

Table 7.S2. Analysis using binary variable for underreporting in longitudinal association between dietary glycemic load at baseline and cardiometabolic risk outcomes after 2 years of follow up in children from the QUALITY cohort, ages 8 to 10 at baseline

	Continuous GL	Tertiles of Glycemic Load		
		1	2	3
Outcome				
BMI z-score				
Mean difference (95% CI)	0.01 (0.001, 0.002)	0	0.14 (-0.06, 0.35)	0.36 (0.15, 0.57)
Adjusted mean difference (95% CI)*	0.009 (0.001, 0.01)	0	0.21 (0.01, 0.42)	0.44 (0.22, 0.66)
Fat mass (%)				
Mean difference (95% CI)	0.06 (0.02, 0.10)	0	1.87 (-0.20, 3.95)	3.11 (0.99, 5.23)
Adjusted mean difference (95% CI)	0.09 (0.05, 0.13)	0	2.52 (0.52, 4.52)	4.36 (2.24, 6.47)
Triglycerides (mmol/L)				
Mean difference (95% CI)	0.001 (-0.001, 0.002)	0	-0.05 (-0.14, 0.04)	0.03 (-0.06, -0.12)
Adjusted mean difference (95% CI)	0.002 (0.0001, 0.004)	0	-0.01 (-0.11, 0.07)	0.08 (-0.01, 0.16)
LDL cholesterol (mmol/L)				
Mean difference (95% CI)	0.0001 (-0.002, 0.002)	0	0.05 (-0.08, 0.17)	0.01 (-0.12, 0.13)
Adjusted mean difference (95% CI)	0.001 (-0.001, 0.004)	0	0.09 (-0.04, 0.22)	0.06 (-0.07, 0.20)
HDL cholesterol (mmol/L)				
Mean difference (95% CI)	-0.0003 (-0.001, 0.001)	0	0.01 (-0.04, 0.06)	-0.03 (-0.08, 0.03)
Adjusted mean difference (95% CI)	-0.0001 (-0.002, 0.0004)	0	0.002 (-0.05, 0.05)	-0.04 (-0.10, 0.01)
SBP z-score				
Mean difference (95% CI)	-0.001 (-0.004, 0.003)	0	-0.03 (-0.20, 0.13)	-0.08 (-0.24, 0.09)
Adjusted mean difference (95% CI)*	-0.004 (-0.004, 0.003)	0	-0.02 (-0.19, 0.14)	-0.08 (-0.25, 0.09)
DBP z-score				
Mean difference (95% CI)	0.0002 (-0.002, 0.002)	0	0.03 (-0.07, 0.13)	0.03 (-0.07, 0.13)
Adjusted mean difference (95% CI)*	-0.0004 (-0.002, 0.002)	0	0.03 (-0.07, 0.13)	0.002 (-0.10, 0.11)

Abbreviations: body mass index: BMI; confidence interval: CI; diastolic blood pressure: DBP; high-density lipoprotein: HDL; low-density lipoprotein: LDL; systolic blood pressure: SBP

All crude models were adjusted for underreporting (ratio of energy intake and estimated energy requirement). All multiple linear regression models were adjusted for age, sex, pubertal vs non-pubertal status, screen time, physical activity (CPM), family income, parent education (4 categories), ratio of energy intake and estimated energy requirement, energy (residual method), fat and protein intake (residuals), season

*Age and sex were only included in the percent fat mass, TG, LDL and HDL models

Interpretation: †Continuous model: every 10 unit increase in GL at baseline is associated with a mean increase in outcome of x. ‡Tertile model: consuming a dietary GL in the highest tertile compared to the lowest reference tertile at baseline is associated with an increased outcome of x after 2 years of follow-up

Postscript to Manuscript 2

The previous manuscript assessed the association between glycemic index and load on cardiovascular risk factors in children. We showed that glycemic load, but not glycemic index was associated with adiposity and blood lipids in children after 2 years of follow-up. Specifically, glycemic load predicted body mass index z-score, percent fat mass, triglycerides and HDL cholesterol in children after 2 years. The strength of the association between glycemic load and these cardiovascular risk outcomes tended to increase with increasing tertiles of glycemic load. Our subsequent analysis assesses the relationship between meal-specific glycemic index and glycemic load with cardiometabolic risk factors.

In addition, in manuscript 2, we conducted preliminary mediation analyses using the Baron and Kenny approach to examine the role of adiposity as a mediator in the glycemic load-blood lipid associations. Results from these analyses suggest that adiposity mediates the glycemic load-triglyceride and glycemic load-HDL cholesterol associations. Further investigation of mediation by adiposity is required, utilizing different mediation analysis methods and will be presented in manuscript 4.

CHAPTER 8: Meal-specific glycemic index and load and cardiovascular risk factors

We expanded our investigation of the association of dietary glycemic index and load and cardiovascular risk factors in children by examining the effect of individual meal glycemic index and load as well as the effect of frequency of high daily glycemic index and load meals. Due to the variation in exergy expenditure throughout the day, children consuming higher glycemic index or load at certain times of the day may have worsened cardiometabolic risk factors. This manuscript is an extension of the previous manuscript (Chapter 7), further decomposing daily diet into meal-specific diet. We therefore set out to examine the effect of individual meal glycemic index and load as well as the frequency of high daily glycemic index and load meals on adiposity, blood lipids and blood pressure in children after 2 years of follow-up.

This study was presented as a poster at the American Heart Association EPI Lifestyle conference and the abstract was published in *Circulation* in March 2019. The manuscript is in preparation as of October 2019 for submission to the *American Journal of Clinical Nutrition*.

MANUSCRIPT 3

Original research article

Association of meal-specific glycemic load on 2-year Cardiovascular Risk Factors in Children

Running head: Meal-specific glycemic load and cardiovascular risk factors

Karine Suissa[1], Andrea Benedetti[1,2,3], Mélanie Henderson[4,5], Katherine Gray-Donald[6], Gilles Paradis[1]

Affiliations:
[1]Department of Epidemiology, Biostatistics, and Occupational Health, McGill University, Montreal, Quebec, Canada
[2]Department of Medicine, McGill University, Montreal, Quebec, Canada
[3]Respiratory Epidemiology and Clinical Research Unit, McGill University Health Centre, Montreal, Quebec, Canada
[4]Research Center of Centre Hospitalier Universitaire Sainte-Justine, Montreal, Canada.
[5]Department of Pediatrics, Faculty of Medicine, Université de Montréal, Montreal, Canada.
[6] School of Dietetics and Human Nutrition, McGill University, Montreal, Quebec, Canada (retired)

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Address for Correspondence:

Gilles Paradis, MD, MSc, FRCPC
Professor and Chair
Department of Epidemiology, Biostatistics and Occupational Health
McGill University - Purvis Hall
1020 Pine Avenue West
Montreal, Quebec, Canada, H3A 1A2
Tel.: 514-398-6259
Fax: 514-398-2373
Email: chair.epid@mcgill.ca

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ABSTRACT

Introduction: A daily diet consisting of high glycemic load (GL) carbohydrates can have long-term effects on body weight and cardiovascular health. However, the GL of certain meals (breakfast, lunch and dinner) may have a different physiological response. Few studies have examined the effect of meal-specific GL and frequency of high GL meals on adiposity and cardiovascular health in children.

Methods: The QUALITY cohort recruited 630 children, ages 8-10 years at baseline with at least one obese parent. Three non-consecutive 24-hour dietary recalls were administered by a dietitian at baseline and individual meal-specific GL scores were calculated using the International table of GI. CV risk factors measured at 2 years of follow-up included continuous values of BMI z-score, percent fat mass, triglycerides, LDL and HDL cholesterol, and systolic and diastolic blood pressure. Linear regressions between meal-specific GI or GL and CV risk factors were conducted, adjusting for important confounders, including underreporting, as well as anthropometric, socio-economic and dietary factors. Secondary analysis consisted of linear regression with number of high GL meals (high GI (70) and GL (20) vs. low) as an ordinal exposure variable.

Results: Mean age at baseline was 9.6 years, with 33% of children overweight or obese. Dinner GL was associated with an increased BMI z-score (ß: 0.007, 95%CI: 0.004, 0.01), percent fat mass (ß: 0.05, 95%CI: 0.02, 0.09), TG (ß: 0.002, 95%CI: 0.0004, 0.03) and decreased HDL cholesterol (ß: -0.001, 95%CI: -0.001, -0.003) but while effect estimates were larger for breakfast and lunch, results were inconclusive. Lunch GI was only associated with increased TG (ß: 0.06, 95%CI: 0.01, 0.11) (Table 3). The number of high GI meals was associated with increased TG and decreased HDL cholesterol.

Conclusion: Dietary GL of dinner meals was associated with increased adiposity and worsened blood lipids in children after 2 years, but results for other mealtimes were inconclusive.
Keywords: glycemic index, glycemic load, children, cardiovascular risk factors, meal-specific

INTRODUCTION

Childhood obesity in Canada has risen dramatically in the last 40 years. Whereas one in four children were overweight or obese in 1978, it is currently one in three according to the most recent Canadian Health Measures Survey.[1] Childhood obesity is associated with metabolic and cardiovascular (CV) risk factors, including metabolic syndrome, type 2 diabetes, and hypertension, and may lead to cardiovascular disease (CVD) in adulthood.[2,3] Understanding the various causes of childhood obesity and cardiovascular risk factors will help plan treatment and prevention efforts. Among a number of known determinants, diet is an important component of cardiovascular health that may influence the progression of CVD risk from childhood to adulthood.

Consuming carbohydrates with high glycemic index is thought to be related to the obesity and metabolic syndrome epidemic.[4] Dietary glycemic index (GI) is a concept proposed by Jenkins et al. as a means of quantifying the differences in the blood glucose response resulting from varying quality of dietary carbohydrates.[5] Glycemic index is the incremental area under the blood glucose curve 2 hours after the ingestion of 50 grams of available carbohydrates compared to an equal amount of glucose.[5] Glycemic load (GL) is an indicator of both quality (GI) and quantity of carbohydrates consumed.[5] High glycemic index meals lead to high postprandial blood glucose and insulin peaks that are associated with increased fat deposit. When nutrient absorption has slowed, the body enters a hypoglycemic state that may increase hunger and energy intake.[6] For example, consuming a high, compared to a low, glycemic index breakfast may have an effect on the quality and size of subsequent meals. In addition, consuming several high glycemic index meals daily may have long-term effects on obesity and cardiovascular risk. On the other hand, consuming a low glycemic index breakfast may help control energy intake during the rest of the day and have long-term benefits on health. In fact, experimental trials have shown that low GI breakfasts lead to increased satiety and lower energy intake during the day particularly in adults and slightly less so in children.[7-10] In addition, two trials have observed a beneficial effect of a consuming a low glycemic index breakfast on cardiometabolic risk factors in adults[11] and children.[12] However, few studies have assessed the meal-specific GI and GL of other meals in children.

Studies that have examined the effects of a low GI/GL breakfast on metabolic risk factors were mostly randomized controlled trials. Given the strict criteria for patient selection and adherence to meal consumption involved in experimental studies, these are not representative of real-world conditions. Therefore, our objective was to study the effect of meal-specific GI/GL on daily energy intake in a real-world setting. We examined the effect of meal-specific GI/GL and number of daily high GI/GL meals on cardiometabolic risk factors in school-aged children with a family history of obesity.

METHODS

Study population

The design and methods of the QUALITY study has been previously described. [13] A total of 630 Caucasian children of Western European ancestry, originally aged 8-10 years, and both biological parents were recruited and, two years later, the follow-up included 564 children (89.5% retention). Children had at least one obese parent (body mass index (BMI) ≥30 kg/m^2 or waist circumference ≥102 cm (men) or ≥88 cm (women)). Children were excluded if their mother was pregnant or the family had plans to move out of province, and if the children 1) had type 1 or type 2 diabetes, 2) had a serious illness, psychological or cognitive disorder, 3) were treated with oral anti-hypertensive medication or steroids, or 4) were following a very restricted diet (<600 kcal/day).

Measurements

Trained dietitians administered three non-consecutive 24h dietary recalls including one weekend day over the telephone within 8-12 weeks following the baseline visit. A small disposable kit of food portion models (for example, a graduated cup, a bowl, etc.) was provided to participants at the baseline hospital visit, in conjunction with a short training and practice session for both children and their parents. Interviews were conducted with the child, and parents helped with food descriptions and cooking details when necessary. The dietary data collected from 613 participants

were entered in the CANDAT Nutrient Analysis Software (Godin and associates, London, Ontario, 2007), which calculates nutrient composition of foods based on the Canadian Nutrition Files.

Glycemic index and GL were assigned to foods in our database using a step-by-step approach. First, each food group that contained less than or equal to 5 grams of carbohydrates per 100 grams were assigned a value of zero.[14] Next, food listed in the International table of GI[15] were assigned the corresponding GI score. Food that were not listed in the International table of GI [15] were assigned a score by identifying the closest nutritionally matching food and assigning its GI score to the unlisted food. [14,16] Finally, every GI score assigned was multiplied by the available carbohydrate content in each food to obtain a GL score. Average GI and GL were obtained for each meal (breakfast, lunch, dinner) for each participant by calculating the sum of the scores of each meal by recall day and then averaging the totals of the 3 dietary recalls.

A standard protocol was followed to collect all anthropometric measurements. A stadiometer was used for height (to the nearest 0.1 cm), and an electronic scale for weight (to the nearest 0.1 kg) with participants dressed in light indoor clothing with no shoes. Height and weight were measured twice, with a third measure obtained if the first two measures differed by 0.2 centimeters or 0.2 kilograms or more. The final values for height and weight were calculated as the average of the two closest measurements. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. Age- and sex-specific BMI z-score (BMIz) was obtained using CDC growth charts[17] Percent body fat was assessed using dual energy X-ray absorptiometry (DEXA, Prodigy Bone Densitometer System, DF-14664, GE Lunar Corporation, Madison, WI, USA). At each clinic visit, blood was collected from both children and parents by venipuncture following an overnight fast. Blood samples were centrifuged, aliquoted and stored at minus 80 Celsius and were analyzed at the Department of Biochemistry of Centre Hospitalier Universitaire Sainte-Justine.[13] Plasma total cholesterol, TG and HDL-cholesterol concentrations were determined on a Synchron LX®20 with Beckman Instruments reagents and expressed as mmol/L. LDL cholesterol was calculated using the Friedewald equation.[18]

Blood pressure was measured on the right arm with the participant in the seated position, after a rest period of a minimum of 5 minutes on an oscillometric instrument (Dinamap XL, model

CR9340, Critikon Company, FL, USA). The mean value of the last three of five consecutive readings that were recorded was used for Systolic Blood Pressure (SBP) and Diastolic Blood Pressure (DBP). Age, sex and height specific z-scores were calculated for SBP and DBP following the Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents.[19]

Physical activity was assessed over a 7-day period using an Actigraph LS 7164 activity monitor (Actigraph LLC, Pensacola, Florida). Accelerometry data were downloaded as 1-min epochs and were processed using standardized quality control and data reduction procedures.[20] Participants were retained if they had a minimum of four or more days with a minimum of 10 hours of wear time, as has been described in more detail elsewhere.[21] For the present study, we used daily step counts to adjust for physical activity. Screen time was assessed by interviewer-administered questionnaire that collected daily hours of television, computer or video game use. Data on family history of disease, highest maternal and paternal education level and household income were collected from parental questionnaires. Sexual maturity was directly observed by trained nurses and scored according to the Tanner stages.[22,23] For our analyses, we categorized children into prepubertal (stage 1) or pubertal (stages 2 and higher).

Exposure and outcome definition

For our study, the outcomes of interest included BMI z-score, percent fat mass, blood lipids including TG, high-density lipoprotein (HDL) and low-density lipoprotein (LDL) cholesterol and SBP z-score and DBP z-score. We assessed two different exposure definitions of GI and GL: 1) continuous GI or GL score for each meal (GI ranging from 15 to 80; GL ranging from 5 to 200); 2) cumulative number of meals per day with a high GI (>70) or GL (≥20) score (categorical variable, ranging from 0 to 3). Skipped meals or meals with no GI/GL score were categorized as low GI/GL.

Statistical analyses

Descriptive statistics are reported as mean (standard deviation (SD)) or median (interquartile range (IQR)) for both baseline and follow-up visits. We used multiple imputation (ice command in STATA version 13.1) to account for missing data of covariates, particularly the physical activity variable that had 15 percent missing data. We estimated multiple linear regression models for each cardiovascular outcome of interest, with continuous meal-specific GI or GL as the independent variable of primary interest, adjusted for important confounders measured at baseline (age, sex, Tanner stage, physical activity, family income, parental education, fat intake (residuals), protein intake (residuals), season, kcal and underreporting (yes vs. no)). For the next analysis we used dummy variables to consider the different levels of exposure. Four dummy variables were created for each level (for example: 1, 2 or 3 high GI/GL meals per day compared to the reference of 0 high GI/GL meals per day) in order to capture non-linear trends between the categories. We used a linear regression to regress the outcome variable on the dummy variables and potential confounders, for each outcome. Sensitivity analyses were conducted to examine the effect of misclassification of exposure due to underreporting on our main results where we reclassified the underreporters with a low GI or GL as high GI or GL. We used STATA version 13.1.

RESULTS

Baseline and follow-up population characteristics are presented in table 1. A total of 630 participants were recruited at baseline with 564 retained for the follow-up visit (n=66 lost to follow-up). The BMI and sex distribution of children remaining at follow-up were not significantly different than baseline. However, at follow-up, children had longer daily screen time, greater percent fat mass and were less physically active compared to baseline (Table 8.1). Baseline characteristics stratified by number of high GL and GI meals per day are presented in Tables 8.S1 to 8.S4. Briefly, among individuals that consumed 2 or more high GI and GL daily, a higher percentage was male and household income was slightly lower compared to individuals that consumed less than 2 high GI or GL meals daily. Children that consumed 2 or more high GL meals per day had an overall greater consumption of protein, fat, saturated fat, fiber and sugar sweetened beverages and were more physically active than those consuming less high GL meals.

Children that consumed a greater number of high GI meals consumed a higher absolute quantity of all macronutrients, less portions of fruits and vegetables, more grains and less milk and alternatives and were also more physically active.

Linear regression showed that neither breakfast nor lunch GL were associated with any cardiometabolic risk outcomes. Dinner GL (interpretation: every 10 unit increase in dinner GL at baseline is associated with a mean increase in outcome of ß) was associated with an increased BMI z-score (ß: 0.007, 95%CI: 0.004, 0.01), percent fat mass (ß: 0.05, 95%CI: 0.02, 0.09), TG (ß: 0.002, 95%CI: 0.0004, 0.03) and decreased HDL cholesterol (ß: -0.001, 95%CI: -0.001, 0.003) but not with LDL, SBP z-score or DBP z-score (Table 10.2). Lunch GI was only associated with increased TG (ß: 0.06, 95%CI: 0.01, 0.11) (Table 8.3).

The number of high GL meals was associated with increased TG (1 high GL meal: mean difference (md)=0.10, 95%CI: 0.003, 0.19 and 2 high GL meals: md=0.17, 95%CI: 0.05, 0.29), whereas consumption of 3 high GI meals was associated with increased TG (md=0.15, 95% CI: 0.006, 0.30) and 1 or 2 high GI meals were associated with decreased HDL cholesterol (md=-0.11 95%CI: -0.18, -0.03 and md=0.09, 95%CI: -0.17, -0.01, respectively) (Tables 8.4-8.5).

Results from our sensitivity analyses revealed that the associations observed in our main analyses of high GI and GL meal frequency may have been attenuated as a result of misclassification of exposure due to underreporting. (Tables 8.S5 and 8.S6). For example, in our main results, consumption of 3 high GL meals daily was not associated with BMI z-score (mean difference: 0.25, 95%CI: -0.14, 0.65) (Table 8.4). When low GL underreporters were reclassified as high GL, there was a 0.63 (95%CI: 0.43, 0.83) BMI z-score difference in those that consumed 3 daily high GL meals compared to none (Table 8.S5).

DISCUSSION

The aim of the present study was to investigate the associations between meal-specific level of GI and GL and the number of high GL or GI meals on cardiovascular risk factors after 2 years in children. We observed an association between a high dinner GL and BMI z-score, percent

fat mass, TG and HDL cholesterol independent of the GL of other meals. As well, the increasing number of daily high GL meals consumed was associated with increasing levels of TG. These results are consistent with a previously conducted study in the same cohort examining the association between average daily GL and these cardiovascular outcomes, however now identifying dinner GL as having the most impact.

We also observed an association between lunch GI and TG as well as the number high GI meals and TG and HDL. In our previous study on average daily GI, we did not observe any associations which we attributed to low variability of the average daily GI variable. In the present study, we decomposed this value into average daily meal-specific GI which enabled us to observe an association with TG and HDL.

We observed a cumulative effect of consuming mostly high GI and GL meals daily on blood lipids after 2 years. Specifically, we observed an association between the consumption of 1 or 2 high GL meals and 3 high GI meals on increased TG. Triglycerides, unlike HDL cholesterol, was affected by the quantity and quality of the carbohydrates consumed rather than only the quality. While it is not clear why TG would be more affected than HDL cholesterol, mechanistically it could reflect the fact that TG tend to decrease between meals, however consuming excessive quantities of sugar will cause TG to accumulate in the blood stream at levels that could not be cleared between meals. [24] Consequently, HDL cholesterol is decreased by the presence of high circulating TG in the blood, because of its role in the clearance of circulating TG.[25] A study by Nicholl et al. observed that breakfast GL was associated with an increased odds of metabolic syndrome in girls, as well as increased TG and decreased HDL.[16] Results from experimental studies have found similar results.[11,27] One randomized crossover trial found no effect of breakfast GI on body fat percent, HDL, LDL and TG, concluding that there was no short term effect of decreasing breakfast GI. [11] A decrease in GI of only one meal per day can have an effect on fasting glucose and satiety which could affect blood lipids and adiposity in the longer term. In fact, another study with a longer intervention of 3 months suggested that there could be a long term of effect of decreasing the meal-specific GI, showing a decrease in TG and LDL. [28]

We observed an association between dinner GL, but not the GI of any meal, and measures of adiposity after 2 years. In a previous study, we observed an association between average daily GL and BMI z-score and percent fat mass.(Chapter 9) This suggests that consuming foods high in GL at dinnertime might have the most harmful effect compared to other meals during the day, due to increased energy storage resulting from decreased energy expenditure. [29] Several authors have discussed the detrimental role of late-night food consumption and high-energy dinner meals on adiposity. In a randomized study, Jakubowicz et al. tested a high-energy breakfast compared to a high-energy dinner meal in a group of obese and overweight women. [30] They observed that the high-energy dinner group had lower satiety, increased hunger and less weight loss compared to the high-energy breakfast group. Similarly, Madjd et al. determined that higher energy consumption at lunch rather than at dinner may be more beneficial for weight loss in overweight and obese women.[31] Studies have also shown that obese children[32] and adult women[33] tend to eat less in the morning and more in the evening compared to lean controls. Studies have also reported that consuming more food in the evening as well as late night eating was associated with a high probability of being overweight or obese.[34-36] However, very few studies have assessed the effect of meal-specific GL on adiposity and cardiovascular risk factors. A study of western Australian adolescents that examined associations between meal-specific GL and metabolic syndrome reported an association between breakfast GL, but not dinner GL, and metabolic syndrome. While this study used the 3-day food record, a strong dietary measurement tool, the cross-sectional nature of their study may have resulted in reverse causation. In addition, their results may not be generalizable to an American population, given the large variation of dietary cultures. Another study of only 6 healthy lean individuals showed an association between high-GI evening meals and postprandial glucose profile.[37] Our results add to this very limited body of evidence, suggesting the importance of consuming low GL meals at dinnertime. Nevertheless, it should be noted that while the breakfast and lunch GL effect estimates were quite larger than dinnertime GL effects, the confidence intervals of the former were too wide to yield any conclusive results.

We assessed the potential bias resulting from misclassification of exposure due to underreporting potentially affecting our high GI and GL frequency models within a series of sensitivity analyses. To this end, we reclassified underreporters with low GI or GL as high GI or GL. We observed that misclassification of exposure was responsible for strong attenuation of our

main results despite statistically adjusting for the underreporting binary variable. While it is not clear how far from the truth the main results are because we did not have a gold standard measure of dietary intake, if our results represented an attenuated version of the truth, this suggests that the truth would involve stronger associations.

Out study has several strengths. The QUALITY cohort data was carefully collected using the most recent measurement tools and provides a large number of covariates, with special attention given to dietary measurements. In addition, unlike other studies, our data allowed us to assess meal specific GI and GL, which cannot be done when using food frequency questionnaire data.

Our study also has limitations. First of all, the 24h diet recall can result in measurement error because it depends on memory and recall, nevertheless, it remains a strong measurement tool for dietary intake, especially when conducted on three or more non-consecutive days. In addition, dietary measurement in the QUALITY study involved parent participation as well as use of disposable containers and rulers to help participants with portion estimations which should reduce recall bias. Moreover, interviews were administered at times that were unannounced and unknown to the participants, which should also considerably reduce reporting bias. While parents could not help in the description of foods that were consumed at school and did not originate from the home, we do not believe that this significantly altered the child's reported intake. In fact, several studies have shown that children of 8 to 10 years of age can report their food intake as reliably as with the help of their parents, particularly on regular weekdays[38-40] In addition, random error resulting from intra-individual variation in daily intake should be minimized by averaging dietary intake reports across three non-consecutive days of interviews. Second, misclassification of exposure due to underreporting may have attenuated our results. To account for differential reporting, we adjusted for underreporting and performed sensitivity analyses to examine the accuracy of our results. Third, although we adjusted for a variety of dietary and non-dietary confounders, there is still a potential for residual confounding by variables strongly correlated with dietary GI or GL that may also explain or mask an association. Finally, our results are principally generalizable to Caucasian children at risk of obesity. Further research examining these associations among children of different ethnic and racial backgrounds would be informative.

CONCLUSION

In our longitudinal cohort of children aged 8-10 years, dietary GL of dinner meals was associated with increased adiposity and worsened blood lipids after 2 years. In addition, the frequency of high GI and GL meals was associated with TG and HDL. Our results serve to further clarify how GL affects cardiometabolic risk factors in children. Consuming an evening meal low in dietary GL can help reduce adiposity and cardiovascular risk factors in children. In addition, decreasing the frequency of high GL meals daily can have beneficial effects on lipid profile in children.

CONTRIBUTIONS

KS designed the research question for this project, conducted the analysis, interpreted results and wrote the manuscript. AB, MH, KGD and GP participated in the research question design (defining outcomes, identifying confounders, determining appropriate analysis methods), reviewed and edited the manuscript.

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Table 8.1. Population characteristics of children in the QUALITY cohort at baseline and first follow-up visit

Characteristic	Baseline n=630	Follow-up n=564
Age (years), mean (SD)	9.6 (0.9)	11.7 (0.9)
Male, %	54.4	55.5
BMI category, %		
Underweight (z-score < -2)	0.3	0.9
Normal weight (z-score ≥ -2 & <1)	56.7	58.3
Overweight (z-score ≥ 1 & < 2)	30.0	28.4
Obese (z-score ≥ 2)	13.0	12.4
Tanner stage, %		
Prepubertal	78.4	33.2
Pubertal	21.6	66.8
Percent fat mass, median (IQR)	25.3 (17.4 to 35.2)	27.8 (19.4 to 36.4)
Screen time, median (IQR), h/d	2.2 (1.3 to 3.7)	2.9 (1.9 to 4.4)
SBP z-score, median (IQR)	-0.79 (-1.26 to -0.35)	-0.85 (-1.37 to -0.39)
DBP z-score, median (IQR)	-1.09 (-1.40 to -0.83)	-1.09 (-1.39 to -0.80)
Triglycerides, median (IQR)	0.7 (0.6 to 1.0)	0.7 (0.5 to 0.9)
HDL cholesterol, median (IQR)	1.2 (1.0 to 1.3)	1.1 (1.0 to 1.3)
LDL cholesterol, median (IQR)	2.3 (2.0 to 2.7)	2.2 (1.9 to 2.6)
Parent education		
no parent with high school diploma	1.4	0.8
1 or 2 parents with high school diploma	6.4	6.4
1 or 2 parents with community college or equivalent	37.8	42.9
1 or 2 parents with university degree	54.4	49.9
Family income, mean (SD)	42,360 (18,574)	48,643 (22,191)
Glycemic index, mean (SD)	52.2 (4.2)	-
Glycemic load, mean (SD)	110.1 (30.8)	-
Carbohydrate intake, mean per day (SD), g	221.3 (56.0)	-
Energy intake, mean per day (SD), kcal	1681.8 (388.4)	-
Sugar-sweetened beverages, median (IQR), ml	67.9 (0.0 to 189.5)	-
Number of snacks, median (IQR)	5 (3 to 6)	-
Physical activity, median (IQR), counts per minute*	559.1 (459.0 to 675.1)	462.3 (374.5 to 587.3)

Table 8.2. Longitudinal association between meal-specific baseline dietary glycemic load and cardiometabolic risk outcomes after 2 years of follow-up in children from the QUALITY cohort

Outcome variable	Crude ß (95% CI)	Adjusted ß (95% CI)
BMI z-score*		
Breakfast	-0.06 (-0.15, 0.03)	-0.07 (-0.17, 0.03)
Lunch	-0.03 (-0.10, 0.05)	-0.03 (-0.12, 0.05)
Dinner	0.008 (0.004, 0.01)	0.007 (0.004, 0.01)
Fat mass (%)		
Breakfast	-0.42 (-1.32, 0.48)	-0.16 (-1.15, 0.83)
Lunch	-0.10 (-0.07, 0.67)	0.28 (-0.59, 1.14)
Dinner	0.05 (0.01, 0.08)	0.05 (0.02, 0.09)
Triglycerides (mmol/L)		
Breakfast	0.03 (-0.005, 0.07)	0.01 (-0.03, 0.06)
Lunch	-0.009 (-0.04, 0.02)	-0.007 (-0.04, 0.03)
Dinner	0.002 (0.001, 0.003)	0.002 (0.0004, 0.03)
LDL cholesterol (mmol/L)		
Breakfast	-0.006 (-0.06, 0.05)	-0.03 (-0.09, 0.03)
Lunch	-0.03 (-0.07, 0.02)	-0.05 (-0.10, 0.006)
Dinner	0.00 (-0.002, 0.002)	0.001 (-0.001, 0.003)
HDL cholesterol (mmol/L)		
Breakfast	-0.001 (-0.02, 0.02)	0.01 (-0.01, 0.04)
Lunch	0.007 (-0.01, 0.03)	0.01 (-0.01, 0.03)
Dinner	-0.001 (-0.002, 0.00)	-0.001 (-0.001, -0.003)
SBP z-score*		
Breakfast	0.05 (-0.03, 0.12)	0.05 (-0.04, 0.13)
Lunch	0.02 (-0.05, 0.08)	-0.003 (-0.08, 0.07)
Dinner	0.0004 (-0.02, 0.003)	-0.001 (-0.004, 0.002)
DBP z-score*		
Breakfast	-0.006 (-0.05, 0.11)	0.002 (-0.05, 0.05)
Lunch	-0.02 (-0.06, 0.02)	-0.02 (-0.07, 0.02)
Dinner	0.00 (-0.002, 0.002)	0.0004 (-0.002, 0.001)

Abbreviations: body mass index: BMI; confidence interval: CI; diastolic blood pressure: DBP; high-density lipoprotein: HDL; low-density lipoprotein: LDL; systolic blood pressure: SBP
High GL defined as GL≥20
Each multiple linear regression model (breakfast, lunch and dinner) was adjusted for age, sex, pubertal status, parent education, family income, physical activity, screen time, fat intake (residual), protein intake (residual), total energy intake (residual methods), underreporting
*Age and sex were not included in the BMI, SBP and DBP z-score models

Interpretation: every 10 unit increase in GL at baseline is associated with a mean increase in outcome of x.

Table 8.3. Longitudinal association between meal-specific dietary glycemic index at baseline and cardiometabolic risk outcomes after 2 years of follow-up in children from the QUALITY cohort

Outcome variable	Crude ß (95% CI)	Adjusted ß (95% CI)
BMI z-score		
Breakfast	-0.01 (-0.15, 0.13)	-0.03 (-0.16, 0.11)
Lunch	0.05 (-0.07, 0.17)	0.08 (-0.04, 0.20)
Dinner	0.06 (-0.07, 0.19)	0.03 (-0.10, 0.16)
Fat mass (%)		
Breakfast	0.18 (-1.21, 1.57)	-0.08 (-1.44, 1.28)
Lunch	0.57 (-0.63, 1.76)	0.72 (-0.45, 1.89)
Dinner	0.12 (-1.17, 1.41)	-0.01 (-1.27, 1.25)
Triglycerides (mmol/L)		
Breakfast	0.06 (-0.004, 0.10)	0.05 (-0.02, 0.11)
Lunch	0.05 (0.01, 0.10)	0.06 (0.01, 0.11)
Dinner	0.002 (-0.05, 0.05)	-0.003 (-0.06, 0.05)
LDL cholesterol (mmol/L)		
Breakfast	-0.02 (-0.10, 0.07)	-0.01 (-0.09, 0.07)
Lunch	0.03 (-0.05, 0.10)	0.01 (-0.06, 0.09)
Dinner	-0.01 (-0.08, 0.06)	0.008 (-0.07, 0.08)
HDL cholesterol (mmol/L)		
Breakfast	0.002 (-0.03, 0.03)	0.007 (-0.03, 0.04)
Lunch	-0.01 (-0.04, 0.02)	-0.01 (-0.04, 0.02)
Dinner	-0.02 (-0.05, 0.01)	-0.02 (-0.05, 0.01)
SBP z-score		
Breakfast	0.02 (-0.08, 0.13)	0.009 (-0.01, 0.12)
Lunch	0.04 (-0.05, 0.13)	0.02 (-0.07, 0.11)
Dinner	0.03 (-0.06, 0.13)	-0.007 (-0.11, 0.09)
DBP z-score		
Breakfast	0.05 (-0.01, 0.11)	0.04 (-0.02, 0.11)
Lunch	0.02 (-0.03, 0.07)	0.006 (-0.05, 0.06)
Dinner	0.03 (-0.03, 0.09)	0.02 (-0.04, 0.08)

Abbreviations: body mass index: BMI; confidence interval: CI; diastolic blood pressure: DBP; high-density lipoprotein: HDL; low-density lipoprotein: LDL; systolic blood pressure: SBP
High GI defined as GI≥70
Each multiple linear regression model (breakfast, lunch and dinner) was adjusted for age, sex, pubertal status, parent education, family income, physical activity, screen time, fat intake (residual), protein intake (residual), underreporting
*Age and sex were not included in the BMI, SBP and DBP z-score models
Interpretation: every 10 unit increase in GI at baseline is associated with a mean increase in outcome of x.

Table 8.4. Adjusted mean difference and 95% CI of the association between number of high daily GL meals on CVD risk factors in school-aged children from the QUALITY cohort

	Number of daily high GL meals (ref=0)			
	0	**1**	**2**	**3**
BMI z-score				
Mean difference	0	0.14 (-0.07, 0.35)	0.15 (-0.11, 0.41)	0.17 (-0.20, 0.55)
Adjusted mean difference	0	0.18 (-0.04, 0.40)	0.20 (-0.08, 0.48)	0.25 (-0.14, 0.65)
Fat mass (%)				
Mean difference	0	0.60 (-1.57, 2.77)	0.34 (-2.29, 2.96)	0.90 (-2.92, 4.73)
Adjusted mean difference	0	1.78 (-0.37, 3.93)	2.25 (-0.53, 5.03)	2.74 (-1.16, 6.63)
Triglycerides (mmol/L)				
Mean difference	0	0.09 (-0.01, 0.18)	0.16 (0.04, 0.27)	0.15 (-0.01, 0.32)
Adjusted mean difference	0	0.10 (0.003, 0.19)	0.17 (0.05, 0.29)	0.15 (-0.01, 0.32)
LDL cholesterol (mmol/L)				
Mean difference	0	-0.02 (-0.14, 0.11)	-0.03 (-0.18, 0.12)	-0.06 (-0.28, 0.16)
Adjusted mean difference	0	-0.04 (-0.17, 0.09)	-0.08 (-0.25, 0.09)	-0.09 (-0.33, 0.14)
HDL cholesterol (mmol/L)				
Mean difference	0	-0.06 (-0.11, -0.005)	-0.08 (-0.15, -0.02)	-0.10 (-0.19, -0.002)
Adjusted mean difference	0	-0.05 (-0.11, 0.002)	-0.07 (-0.14, 0.002)	-0.09 (-0.18, 0.01)
SBP z-score				
Mean difference	0	0.18 (0.005, 0.35)	0.12 (-0.09, 0.32)	-0.16 (-0.46, 0.14)
Adjusted mean difference	0	0.15 (-0.03, 0.32)	0.02 (-0.20, 0.25)	-0.22 (-0.54, 0.09)
DBP z-score				
Mean difference	0	0.05 (-0.05, 0.15)	0.08 (-0.05, 0.20)	-0.05 (-0.23, 0.14)
Adjusted mean difference	0	0.05 (-0.06, 0.16)	0.06 (-0.08, 0.19)	-0.04 (-0.23, 0.15)

Abbreviations: body mass index: BMI; confidence interval: CI; diastolic blood pressure: DBP; high-density lipoprotein: HDL; low-density lipoprotein: LDL; systolic blood pressure: SBP
High GL defined as GL≥20
Each multiple linear regression models included breakfast, lunch, dinner was adjusted for age, sex, pubertal status, parent education, family income, physical activity, screen time, fat intake (residual), protein intake (residual), total energy intake, underreporting
*Age and sex were not included in the BMI, SBP and DBP z-score models

Table 8.5. Adjusted mean difference and 95% CI of the effect of number of high daily GI meals on CVD risk factors in school-aged children from the QUALITY cohort

	Number of daily high GI meals (ref=0)			
	0	**1**	**2**	**3**
BMI z-score				
Mean difference	0	0.20 (-0.12, 0.52)	0.26 (-0.05, 0.58)	0.18 (-0.17, 0.58)
Adjusted mean difference	0	0.15 (-0.16, 0.47)	0.24 (-0.08, 0.56)	0.12 (-0.23, 0.41)
Fat mass (%)				
Mean difference	0	1.79 (-1.37, 4.95)	1.63 (-1.50, 4.75)	1.48 (-1.96, 4.92)
Adjusted mean difference	0	2.05 (-1.06, 5.15)	2.32 (-0.75, 5.40)	1.31 (-2.11, 4.73)
Triglycerides (mmol/L)				
Mean difference	0	0.11 (-0.02, 0.25)	0.06 (-0.07, 0.20)	0.19 (0.04, 0.34)
Adjusted mean difference	0	0.07 (-0.06, 0.21)	0.06 (-0.07, 0.19)	0.15 (0.006, 0.30)
LDL cholesterol (mmol/L)				
Mean difference	0	0.04 (-0.14, 0.22)	0.08 (-0.10, 0.26)	0.07 (-0.13, 0.27)
Adjusted mean difference	0	0.02 (-0.17, 0.20)	0.04 (-0.14, 0.23)	0.05 (-0.16, 0.25)
HDL cholesterol (mmol/L)				
Mean difference	0	-0.11 (-0.18, -0.03)	-0.09 (-0.17, -0.01)	-0.08 (-0.17, 0.002)
Adjusted mean difference	0	-0.11 (-0.18, -0.03)	-0.09 (-0.17, -0.01)	-0.09 (-0.17, 0.004)
SBP z-score				
Mean difference	0	-0.03 (-0.27, -0.22)	0.02 (-0.23, 0.26)	0.02 (-0.25, 0.29)
Adjusted mean difference	0	-0.12 (-0.37, 0.13)	-0.04 (-0.29, 0.21)	-0.11 (-0.39, 0.16)
DBP z-score				
Mean difference	0	0.11 (-0.04, 0.26)	0.13 (-0.02, 0.28)	0.06 (-0.11, 0.22)
Adjusted mean difference	0	0.09 (-0.06, 0.24)	0.11 (-0.03, 0.26)	-0.01 (-0.17, 0.16)

Abbreviations: body mass index: BMI; confidence interval: CI; diastolic blood pressure: DBP; high-density lipoprotein: HDL; low-density lipoprotein: LDL; systolic blood pressure: SBP
High GI defined as GI≥70
Each multiple linear regression models included breakfast, lunch, dinner was adjusted for age, sex, pubertal status, parent education, family income, physical activity, screen time, fat intake (residual), protein intake (residual), underreporting
*Age and sex were not included in the BMI, SBP and DBP z-score models

Supplemental material

Table 8.S1. Population characteristics of children in the QUALITY cohort at the baseline visit stratified by numb

	Number of daily high GL meals		
	0 (n=106)	**1 (n=183)**	**2 (n=120)**
Age (years), mean (SD)	9.4 (0.9)	9.6 (0.9)	9.7 (0.9)
Male, %	42.5	49.2	68.3
BMI category, %			
Underweight (z-score < -2)	0	0	0
Normal weight (z-score ≥ -2 & <1)	56.6	53.0	58.3
Overweight (z-score ≥ 1 & < 2)	29.3	32.8	28.3
Obese (z-score ≥ 2)	14.2	14.2	13.3
Tanner stage, %			
Prepubertal	80.0	76.5	76.7
Pubertal	20.0	23.5	23.3
Percent fat mass, median (IQR)	25.0 (17.6 to 36.7)	26.6 (18.6 to 34.3)	24.2 (15.8 to 33
Screen time, median (IQR), h/d	4.9 (2.8 to 8.5)	4.7 (2.9 to 8.0)	5.9 (3.5 to 9.0
SBP z-score, median (IQR)	-0.9 (-1.2 to -0.4)	-0.8 (-1.2 to -0.2)	-0.9 (-1.4 to -0.
DBP z-score, median (IQR)	-1.1 (-1.4 to -0.8)	-1.1 (-1.4 to -0.8)	-1.2 (-1.5 to -0.
Triglycerides, median (IQR), mmol/L	0.7 (0.6 to 0.9)	0.7 (0.6 to 1.0)	0.8 (0.6 to 1.0
LDL cholesterol, median (IQR), mmol/L	2.3 (2.0 to 2.6)	2.4 (2.0 to 2.8)	2.2 (1.9 to 2.7
HDL cholesterol, median (IQR), mmol/L	1.2 (1.0 to 1.3)	1.1 (1.0 to 1.4)	1.1 (1.0 to 1.3
Parent education			
no parent with high school diploma	1.0	2.2	0.0
1 or 2 parents with high school diploma	6.7	2.2	9.2
1 or 2 parents with community college or equivalent	41.0	27.3	41.7
1 or 2 parents with university degree	51.4	68.3	49.2
Family income, mean (SD), $	44,151 (19,309)	45,140 (17,898)	39,690 (17,314

Table 8.S2. Dietary and physical activity characteristics of children in the QUALITY cohort at the baseline visit of high GL meals

	Number of daily high GL meals		
	0 (n=106)	**1 (n=183)**	**2 (n=120)**
Glycemic load, mean (SD)	84.5 (18.5)	105.4 (19.6)	130.4 (26.0)
Glycemic index, mean (SD)	50.2 (3.8)	51.8 (4.0)	53.1 (3.8)
Carbohydrate intake, mean per day (SD), g	179.5 (38.9)	215.3 (37.2)	259.2 (49.0)
Energy intake, mean per day (SD), kcal	1,431 (310)	1,638 (286.8)	1,914 (341.0)
Protein intake, mean per day (SD), g	64.5 (19.8)	66.5 (17.4)	72.4 (18.5)
Fat intake, mean per day (SD), g	52.4 (16.2)	59.3 (16.6)	68.3 (17.2)
Saturated fat intake, mean per day (SD), g	19.1 (7.1)	21.4 (6.9)	23.8 (7.4)
Fruits and vegetable, mean per day (SD), portions	3.9 (1.8)	4.3 (1.9)	4.7 (2.3)
Grains, mean per day (SD), portions	3.9 (1.2)	4.6 (1.4)	5.6 (1.5)
Milk and alternative, mean per day (SD), portions	1.9 (1.0)	1.9 (0.9)	1.9 (0.9)
Meat and alternative, mean per day (SD), portions	1.9 (0.9)	1.8 (0.8)	2.1 (0.9)
Fiber, mean per day (SD), g	11.9 (3.7)	13.1 (3.7)	14.9 (4.3)
Sugar-sweetened beverages, median (IQR), ml	65.2 (99.1)	106.0 (126.6)	143.9 (143.9)
Number of snacks, median (IQR)	5 (4- 7)	5 (3- 6)	5 (3- 6)
Physical activity, median (IQR), counts per minute*	544 (456- 672)	535 (447- 656)	573 (475- 701)

Table 8.S3. Population characteristics of children in the QUALITY cohort at the baseline visit stratified by numb

	Number of daily high GI m		
	0 (n=141)	**1 (n=201)**	**2 (n=**
Age (years), mean (SD)	9.5 (0.9)	9.6 (0.9)	9.5 (
Male, %	44.7	44.1	47.
BMI category, %			
Underweight (z-score < -2)	0	0	0
Normal weight (z-score ≥ -2 & <1)	61.7	52.5	55.
Overweight (z-score ≥ 1 & < 2)	30.5	32.2	27.
Obese (z-score ≥ 2)	7.8	15.4	16.
Tanner stage, %			
Prepubertal	80.9	75.6	77.
Pubertal	19.2	24.4	22.
Percent fat mass, median (IQR)	25.0 (16.7 to 32.2)	27.4 (19.7 to 36.3)	27.3 (18.2
Screen time, median (IQR), h/d	5.5 (2.8 to 8.0)	6.6 (3.2 to 8.8)	6.1 (3.5
SBP z-score, median (IQR)	-0.9 (-1.3 to -0.4)	-0.7 (-1.2 to -0.2)	-0.9 (-1.4
DBP z-score, median (IQR)	-1.1 (-1.4 to -0.8)	-1.1 (-1.4 to -0.8)	-1.1 (-1.4
Triglycerides, median (IQR), mmol/L	0.8 (0.6 to 0.9)	0.9 (0.6 to 1.0)	0.8 (0.5
LDL cholesterol, median (IQR), mmol/L	2.4 (2.0 to 2.8)	2.3 (1.9 to 2.7)	2.3 (2.0
HDL cholesterol, median (IQR), mmol/L	1.2 (1.1 to 1.4)	1.2 (1.0 to 1.3)	1.1 (1.0
Parent education			
no parent with high school diploma	0.7	1.0	2.2
1 or 2 parents with high school diploma	3.6	6.0	6.7
1 or 2 parents with community college or equivalent	31.9	32.3	41.
1 or 2 parents with university degree	63.8	60.7	50.
Family income, mean (SD), $	43,674 (18,987)	44,512 (17,094)	41,653 (1

Table 8.S4. Dietary and physical activity characteristics of children in the QUALITY cohort at the baseline visit of high GI meals

	Number of daily high GI meals		
	0 (n=141)	**1 (n=201)**	**2 (n=90)**
Glycemic load, mean (SD)	102.7 (29.7)	111.1 (28.2)	130.4 (26.0
Glycemic index, mean (SD)	48.5 (2.8)	51.0 (2.9)	56.1 (2.6)
Carbohydrate intake, mean per day (SD), g	223.2 (58.7)	226.0 (54.8)	229.1 (53.5
Energy intake, mean per day (SD), kcal	1,704 (386)	1,708 (389.6)	1,717 (382
Protein intake, mean per day (SD), g	72.2 (20.2)	68.1 (18.3)	66.6 (17.9)
Fat intake, mean per day (SD), g	60.9 (18.7)	61.6 (18.3)	61.9 (18.4)
Saturated fat intake, mean per day (SD), g	19.1 (7.1)	21.8 (7.3)	21.9 (7.2)
Fruits and vegetable, mean per day (SD), portions	4.8 (2.0)	4.4 (2.1)	4.0 (1.9)
Grains, mean per day (SD), portions	4.4 (1.5)	4.9 (1.5)	5.2 (1.7)
Milk and alternative, mean per day (SD), portions	2.2 (1.0)	1.8 (0.9)	1.7 (0.7)
Meat and alternative, mean per day (SD), portions	2.0 (0.9)	1.9 (0.8)	1.9 (0.8)
Fiber, mean per day (SD), g	14.0 (4.1)	13.6 (4.4)	13.3 (3.9)
Sugar-sweetened beverages, median (IQR), ml	96.2 (122.6)	113.1 (132.7.6)	137.7 (154.2
Number of snacks, median (IQR)	5 (3- 6)	5 (3 to 6)	5 (3 to 7)
Physical activity, median (IQR), counts per minute*	593.5 (464.2- 680.3)	589.3 (450.7 to 676.5)	580.9 (470.7 to

Table 8.S5. Sensitivity analysis with adjusted mean difference and 95% CI of the effect of number of high daily GL meals on CVD risk factors in school-aged children in Quebec with underreporters reclassified as high GL

	Number of daily high GL meals (ref=0)			
	0	**1**	**2**	**3**
BMI z-score				
Mean difference	0	0.40 (0.22, 0.59)	0.44 (0.26, 0.63)	0.67 (0.47, 0.87)
Adjusted mean difference	0	0.38 (0.19, 0.58)	0.43 (0.24, 0.63)	0.63 (0.43, 0.83)
Fat mass (%)				
Mean difference	0	3.51 (1.63, 5.39)	3.39 (1.52, 5.26)	6.61 (4.58, 8.63)
Adjusted mean difference	0	3.72 (1.84, 5.60)	4.18 (2.23, 6.12)	6.51 (4.53, 8.50)
Triglycerides (mmol/L)				
Mean difference	0	0.06 (-0.02, 0.14)	0.12 (0.04, 0.20)	0.16 (0.07, 0.24)
Adjusted mean difference	0	0.07 (-0.02, 0.15)	0.12 (0.04, 0.21)	0.14 (0.05, 0.23)
LDL cholesterol (mmol/L)				
Mean difference	0	0.05 (-0.05, 0.16)	0.10 (-0.01, 0.21)	0.06 (-0.06, 0.17)
Adjusted mean difference	0	0.05 (-0.06, 0.17)	0.11 (-0.01, 0.22)	0.09 (-0.03, 0.21)
HDL cholesterol (mmol/L)				
Mean difference	0	-0.05 (-0.10, -0.01)	-0.08 (-0.13, -0.03)	-0.10 (-0.15, -0.05)
Adjusted mean difference	0	-0.03 (-0.08, 0.02)	-0.06 (-0.11, -0.01)	-0.07 (-0.12, -0.02)
SBP z-score				
Mean difference	0	0.29 (0.14, 0.43)	0.17 (0.02, 0.32)	-0.03 (-0.18, 0.13)
Adjusted mean difference	0	0.25 (0.10, 0.40)	0.07 (-0.08, 0.23)	-0.05 (-0.21, 0.11)
DBP z-score				
Mean difference	0	0.04 (-0.05, 0.14)	0.06 (-0.03, 0.15)	-0.06 (-0.16, 0.04)
Adjusted mean difference	0	0.04 (-0.05, 0.14)	0.04 (-0.06, 0.13)	-0.07 (-0.17, 0.03)

Abbreviations: body mass index: BMI; confidence interval: CI; diastolic blood pressure: DBP; high-density lipoprotein: HDL; low-density lipoprotein; systolic blood pressure: SBP
High GL defined as GL≥20
Each multiple linear regression models included breakfast, lunch, dinner was adjusted for age, sex, pubertal status, parent education, family income, physical activity, screen time, fat intake (residual), protein intake (residual), total energy intake, underreporting
*Age and sex were not included in the BMI z-score, SBP z-score and DBP z-score models

Table 8.S6. Sensitivity analysis for adjusted mean difference and 95% CI of the effect of number of high daily GI meals on CVD risk factors in school-aged children in Quebec with underreporters reclassified as high GI

	Number of daily high GI meals (ref=0)			
	0	**1**	**2**	**3**
BMI z-score				
Mean difference	0	0.44 (0.27, 0.61)	0.52 (0.35, 0.69)	0.44 (0.26, 0.62)
Adjusted mean difference	0	0.41 (0.23, 0.59)	0.50 (0.32, 0.67)	0.37 (0.19, 0.56)
Fat mass (%)				
Mean difference	0	5.06 (3.36, 6.76)	4.89 (3.20, 6.58)	4.76 (3.00, 6.52)
Adjusted mean difference	0	5.04 (3.31, 6.78)	5.03 (3.31, 6.74)	3.84 (2.04, 5.65)
Triglycerides (mmol/L)				
Mean difference	0	0.09 (0.02, 0.16)	0.06 (-0.01, 0.14)	0.14 (0.06, 0.21)
Adjusted mean difference	0	0.06 (-0.01, 0.14)	0.08 (0.01, 0.16)	0.11 (0.03, 0.19)
LDL cholesterol (mmol/L)				
Mean difference	0	0.03 (-0.07, 0.12)	0.07 (-0.03, 0.17)	0.07 (-0.03, 0.17)
Adjusted mean difference	0	0.04 (-0.06, 0.15)	0.08 (-0.02, 0.18)	0.09 (-0.02, 0.19)
HDL cholesterol (mmol/L)				
Mean difference	0	-0.09 (-0.13, -0.04)	-0.06 (-0.10, -0.02)	-0.07 (-0.12, -0.03)
Adjusted mean difference	0	-0.07 (-0.12, -0.03)	-0.06 (-0.09, 0.001)	-0.05 (-0.09, -0.002)
SBP z-score				
Mean difference	0	0.12 (-0.02, 0.25)	0.18 (0.04, 0.31)	0.13 (-0.003, 0.27)
Adjusted mean difference	0	0.10 (-0.04, 0.24)	0.20 (0.06, 0.33)	0.05 (-0.09, 0.20)
DBP z-score				
Mean difference	0	0.03 (-0.05, 0.11)	0.05 (-0.03, 0.13)	-0.03 (-0.11, 0.06)
Adjusted mean difference	0	0.04 (-0.05, 0.12)	0.07 (-0.02, 0.15)	-0.07 (-0.15, 0.02)

Abbreviations: body mass index: BMI; confidence interval: CI; diastolic blood pressure: DBP; high-density lipoprotein: HDL; low-density lipoprotein; systolic blood pressure: SBP
High GI defined as GI≥70
Each multiple linear regression models included breakfast, lunch, dinner was adjusted for age, sex, pubertal status, parent education, family income, physical activity, screen time, fat intake (residual), protein intake (residual), underreporting
*Age and sex were not included in the BMI z-score, SBP z-score and DBP z-score models

Postscript to Manuscript 3

This study identifies an association between increasing dinnertime glycemic load and worsened cardiovascular risk factors in children. Specifically, we discovered that dinnertime glycemic load was associated with increased adiposity and worsened blood lipids after 2 years suggesting that consuming foods high in GL at dinnertime might have the most harmful effect compared to other meals during the day. These results further contribute to understanding the role of dietary glycemic load in cardiovascular risk in children.

CHAPTER 9: Adiposity as a mediator of dietary glycemic load and cardiovascular risk factors in children

This manuscript is intended to further explore the results from the mediation analyses conducted in the second manuscript (Chapter 7). No other study has examined the role of adiposity in the glycemic load and cardiovascular risk associations. In this manuscript, we aimed to compare the conventional approach and the causal approach using marginal structural models with inverse probability weights to examine adiposity as a mediator in the association between baseline dietary glycemic load and lipid profile after 2 years. This manuscript has been submitted for publication to the *International Journal of Obesity* in November 2019.

MANUSCRIPT 4

A mediation analysis on the relationship between dietary glycemic load, obesity and cardiovascular risk factors in preschool children

Karine Suissa[1], Andrea Benedetti[1,2,3], Mélanie Henderson [4,5], Katherine Gray-Donald[6], Gilles Paradis[1]

Affiliations:

[1]Department of Epidemiology, Biostatistics, and Occupational Health, McGill University, Montreal, Quebec, Canada

[2]Department of Medicine, McGill University, Montreal, Quebec, Canada

[3]Respiratory Epidemiology and Clinical Research Unit, McGill University Health Centre, Montreal, Quebec, Canada

[4]Research Center of Centre Hospitalier Universitaire Sainte-Justine, Montreal, Canada.

[5]Department of Pediatrics, Faculty of Medicine, Université de Montréal, Montreal, Canada.

[6] School of Dietetics and Human Nutrition, McGill University, Montreal, Quebec, Canada (retired)

Word Count: 3,440

Address for Correspondence:

Gilles Paradis, MD, MSc, FRCPC
Professor and Chair
Department of Epidemiology, Biostatistics and Occupational Health
McGill University - Purvis Hall
1020 Pine Avenue West
Montreal, Quebec, Canada, H3A 1A2
Tel.: 514-398-6259
Fax: 514-398-2373
Email: chair.epid@mcgill.ca

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ABSTRACT

Adiposity may mediate the effect of dietary glycemic load (GL) on lipid profile in children. We compare two approaches to examine mediation by adiposity in the association between dietary GL and lipid profile after 2 years. The QUALITY cohort includes 630 children, 8-10 years at recruitment with at least one obese parent with 2-year follow-up. Three baseline 24-hour dietary recalls were administered by a dietitian at baseline. Child and parent characteristics were obtained through direct measurement or questionnaires. Adiposity, including BMI z-score and percent fat mass, were the mediators considered. A conventional approach using the Baron and Kenny method was used. A causal approach using marginal structural models (MSM) was used to estimate the controlled direct effect. Mean age at baseline was 9.6 years and 33% were overweight or obese. Both methods revealed that the effect of GL on TG and HDL cholesterol was mediated by adiposity and did not show strong evidence of a direct effect (weighted MSM: TG:β=0.06, 95%CI=-0.01,0.12; HDL:β=-0.01, 95%CI=-0.04,0.03; conventional method TG:β=0.03, 95%CI=0.003,0.06; HDL:β=-0.02, 95%CI=-0.03,-0.001). In conclusion, adiposity contributes substantially to the association between GL and blood lipids. The choice of mediation analysis method should be based on the fulfillment of conditions of each individual method.

INTRODUCTION

The glycemic index (GI) of foods reflects their effect on postprandial glycemia whereas the glycemic load (GL) represents the glycemic index multiplied by the quantity of carbohydrate ingested. Consuming excessive quantities of foods high in glycemic index has been shown to have harmful effects on weight and blood lipids in adults[1-4] and children.[5,6] Unhealthy blood lipid levels in childhood can have long-term detrimental effects on health, including atherosclerosis, cardiovascular disease and diabetes.[7-9] Childhood obesity also has short-term metabolic and cardiovascular (CV) effects, including increased fasting insulin and triglycerides (TG), lowered high-density lipoprotein (HDL) cholesterol and increased blood pressure.[10] Childhood obesity has been associated with the development of type 2 diabetes, and hypertension in children and adolescents, and may lead to cardiovascular diseases (CVD) later in life.[11-13] However, it is not known whether the GL-blood lipid pathway is mediated by adiposity.

Several approaches for conducting mediation analysis have been proposed. The conventional method by Baron and Kenny, a statistical adjustment method for total and direct effects is useful when certain conditions are met such as the absence of unmeasured confounding.[14] However, the Baron and Kenny approach can induce collider stratification bias when adjusting for intermediate variables.[15] Given that the conventional methods for assessing the direct effect produces an unbiased estimate of the controlled direct effect (CDE) only under very specific conditions,[16] it may not be appropriate in all situations. Using marginal structural models (MSM) with inverse probability weights (IPW) to control for confounders may allow for the identification of the direct effect, should all conditions for causal inference be met, including consistency, positivity and exchangeability.[17] Marginal structural models with IPW can be used for causal mediation analysis that adjust for exposure-outcome and mediator-outcome confounders by weighting. The use of IPW to adjust for confounding is done by fitting a model that regresses the outcome on the exposure and weighs each observation by the inverse probability of the observed exposure level given the observed value of confounders.[18] Still, restrictions and strict assumptions are challenges of this approach.

To our knowledge, no study has examined the mediator role of adiposity in the longitudinal association between GL and blood lipid. The aim of this study was to assess whether

the effects of GL on blood lipid levels after 2 years in school-aged children are mediated by adiposity, including measures of BMI z-score and percent fat mass. We compared results obtained using the conventional Baron and Kenny method for mediation analysis to those obtained using marginal structural models with inverse probability weights to adjust for confounders that may cause bias when simple statistical adjustment is used as in conventional mediation analysis.

METHODS

Study population

The design and methods of the QUALITY study have been described elsewhere.[19] Briefly, 630 children 8-10 years of age and both of their biological parents, at least one of whom was obese, were recruited and, two years later 564 children were followed-up (89.5% retention).

Measurements

Trained dietitians conducted interviews of three unannounced non-consecutive 24h dietary recalls including one weekend day within 8-12 weeks following the baseline visit. At baseline, families were provided with a small disposable kit of food portion models (for example, a graduated cup, a bowl, etc.) and offered a short training with a dietitian on how to answer a 24h diet recall. Interviews were conducted by phone with the child. Parents were only involved to help with food descriptions and cooking details when necessary, to improve the completeness of the recall.[20] The dietary data collected from 613 participants were entered in the CANDAT Nutrient Analysis Software (Godin and associates, London, Ontario, 2007), a software which calculates nutrient composition of foods based on the Canadian Nutrition Files.

We assigned GI and GL by first assigning a value of zero to each food group that contained less than or equal to 5 grams of carbohydrate per 100 grams. [21] When a food was listed in the International table of GI, [22] we used the corresponding GI score, however when the food did not have a preassigned GI value in the International table of GI, [22] its nutritional value was assessed by trained nutritionists and we assigned a GI based on the closest nutritionally matching food.[21,23]

Finally, every GI value was multiplied by the amount of carbohydrate ingested to obtain a GL score. We obtained an average daily GL for each participant by calculating the sum of the GL scores by recall day and then averaging the totals of the 3 dietary recalls.

A standardized protocol was used to collect anthropometric measurements. Participants were dressed in light indoor clothing with no shoes; height was measured using a stadiometer (to the nearest 0.1 cm), and weight using an electronic scale (to the nearest 0.1 kg). Height and weight were measured twice, and if these measures differed by 0.2 centimeters or 0.2 kilograms or more, a third measure was obtained. The final value was the average of the two closest measurements. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. Age- and sex-specific BMI z-scores were obtained using CDC growth charts. [24] Percent body fat was assessed using dual energy X-ray absorptiometry (DEXA, Prodigy Bone Densitometer System, DF-14664, GE Lunar Corporation, Madison, WI, USA). At each clinic visit, blood was collected from both children and parents by venipuncture following an overnight fast. Blood samples were centrifuged, aliquoted and stored at minus 80 Celsius and were analyzed at the Department of Biochemistry at Centre Hospitalier Universitaire Sainte-Justine.[9] Plasma total cholesterol, TG and HDL-cholesterol concentrations were determined on a Synchron LX®20 with Beckman Instruments reagents and expressed as mmol/L.

Physical activity was measured for 7 days using an Actigraph LS 7164 activity monitor (Actigraph LLC, Pensacola, Florida). Accelerometry data were downloaded as 1-min epochs and were processed using standardized quality control and data reduction procedures. [25] Participants were retained if they had a minimum of four or more days with a minimum of 10 hours of wear time, as has been described in more detail elsewhere. [26] In our analyses, we used daily step counts to adjust for physical activity. Screen time was assessed by interviewer-administered questionnaire that collected daily hours of television, computer or video game use. Data on family history of disease, highest maternal and paternal education level and household income were collected from parental questionnaires. Sexual maturity was observed by trained nurses and scored according to the Tanner stages[27,28] For our analyses, we categorized children into prepubertal (stage 1) or pubertal (stages 2 and higher).

Exposure, mediator and outcome definition

For our study, the outcomes of interest included blood lipids including TG and high-density lipoprotein (HDL) cholesterol measured at the 2-year follow-up visit. The indicators of adiposity that served as mediators were baseline BMI z-score and percent fat mass. We assumed that the 24H recall reflected habitual dietary intake. GI and GL were the independent variables and were measured at baseline.

Statistical analyses

Descriptive statistics are reported as mean (standard deviation (SD)) or median (interquartile range (IQR)) for both baseline and follow-up visits. To account for missing data of covariates, particularly the physical activity variable that had 15 percent missing data, we used multiple imputation with a total of 15 imputations (Proc MI in SAS version 9.3) analyzed by linear regression and pooled using Proc MIANALYZE in SAS. We estimated multiple linear regression models for each outcome of interest, with GI or GL (adjusted for total energy intake using the residual method[29]) as the independent variable of primary interest, adjusted for important baseline confounders (age, sex, Tanner stage, physical activity, family income, parental education, fat intake (residuals), protein intake (residuals), season, and underreporting (ratio of energy intake and estimated energy requirement)[30]). We assessed linearity of the associations of interest by using restricted cubic regression splines. We tested for interactions between the exposure variable GL with continuous BMI z-score and percent fat mass by introducing an interaction term in adjusted models.

We assessed mediation by adiposity (BMI z-score and percent fat mass) with the conventional Baron and Kenny method.[14] First, we estimated the total effect of GI and GL on TG and HDL on the additive scale (note that X hereby denotes both GI and GL and Y hereby denotes different outcomes including TG and HDL). To this end, we regressed Y_i on X_i and confounders (C_i) as such:

$$E[Y|X,C] = \beta_0 + \beta_1 X_i + \beta_2 C_i \qquad \text{(Model 1)}$$

β_1 from model 1 will be the estimate of the total effect provided that the measured confounders are sufficient to control for the confounders of the X-Y relation. Second, we estimated the direct effect of X on Y using the conventional approach described by Baron and Kenny.[14] For this, we regressed each outcome Y on X, C and adiposity (the mediator M) by fitting a linear regression model as such:

$$E[Y|X,C,M] = \beta_0 + \beta_1 X_i + \beta_2 C_i + \beta_3 M_i \qquad \text{(Model 2)}$$

β_1 from model 2 will be the estimate of the direct effect of X that is not mediated through M, provided that the measured confounders that are adjusted for are sufficient to control for the confounders of the relation between X and Y. Third, we tested for interaction by including interaction terms between X and M in model 2, and because these terms were not statistically significant they were dropped from the model.

Next, we assessed mediation following the causal approach: For this, we computed the controlled direct effect using a weighted generalized estimating equation (GEE) to estimate the weighted marginal structural model (MSM), an approach proposed by VanderWeele[31] and Valeri[32] for continuous exposure, mediators and outcomes.[33] The following model was fitted:

$$g(\mu) = \beta_0 + \beta_1 X_i + \beta_2 M_i + \beta_3 A_i M_i \qquad \text{(Model 3)}$$

where g was a monotone link function. In this case, the continuous outcome followed a linear link function. Inverse probability weights were used to balance covariates and hence control for confounding between X and Y and M and Y. Weights were constructed for both exposure variables (glycemic index and glycemic load) and the mediators (continuous BMI z-score and percent fat mass). We used stabilized weights, which are preferred to standard weights because they are considered more stable; and because of the continuous nature of X and M, unstabilized weights would have infinite variance.[18] For the continuous exposure and mediator variables, we used the marginal average density function of X in the numerator and the marginal density function of X conditional on C as the denominator for the X-Y weights and repeated the same method for the M-Y weights.[18] The product of the two stabilized weights calculated were used in the MSM.

The controlled direct effect for a change in exposure from level x^* to level x was obtained as follows with estimates from the final weighted model [3]:

$$CDE = (\beta_1+\beta_3 m)(x- x^*)$$

The CDE measures how much the mean of the outcome would change if the mediator were controlled at level m uniformly in the population but the exposure were changed from level x^* to level x. Although sometimes unrealistic, a requirement for the CDE is that an intervention be effective at setting every subject to having the same value of the mediator. In general, m would be set as the mean BMI z-score or percent fat mass in the study sample. For the purpose of this study, CDE was equal to β_1 because the interaction term β_3 was not significant.

Finally, we compared the estimates of the direct effect obtained using the traditional mediation analysis results with those obtained using MSM and IPW.

We used SAS version 9.3 for analyses.

RESULTS

Population characteristics at baseline and follow-up are shown in Table 1. A total of 66 children were lost to follow-up among the 630 baseline participants. No significant differences were observed between the children remaining in the sample at the follow-up visit and those lost to follow-up with respect to age, BMI z-score and sex. Compared to baseline, at the 2-year follow-up visit, children had a higher percent fat mass, had longer screen time per day and were less physically active (Table 9.1).

Each 100-unit increase in glycemic load is associated with a 0.06 mmol/L (95%CI: 0.02, 0.09) increase in triglycerides after 2 years (Table 9.2, Figure 9.1). Using the conventional method for mediation analysis by BMI z-score, the point estimate of the direct effect of GL and TG after two years was slightly attenuated to 0.04 (95%CI: 0.01, 0.07). Using MSM with IPW, the direct effect of GL on triglycerides was further attenuated to 0.01 mmol/L (95%CI: -0.01, 0.02). The was no conclusive evidence of an association between GL and LDL cholesterol.

The total effect of glycemic load on HDL cholesterol was -0.02 (95%CI: -0.04, -0.01) indicating that a 100-unit increase in glycemic load is associated with a decrease in HDL by 0.02 mmol/L after 2 years (Table 9.2). Using the conventional method for mediation analysis by BMI z-score, the direct effect of GL and HDL cholesterol after two years was -0.01 (95%CI: -0.03, 0.01). Using MSM with IPW, the direct effect of GL on HDL was 0.01 mmol/L (95%CI: -0.002, 0.01).

In the models using percent fat mass as mediator (Table 9.3), the conventional method showed an association of GL and TG after two years that was attenuated to 0.03 (95%CI: 0.003, 0.06). Using MSM with IPW, the direct effect of glycemic load on triglycerides remained unchanged at 0.06 mmol/L (95%CI: -0.01, 0.12). For HDL cholesterol, the conventional method resulted in an attenuated association of GL and HDL cholesterol after two years of -0.02 (95%CI: -0.03, -0.001). Using MSM with IPW, the direct effect of GL on HDL cholesterol was further attenuated to -0.01 mmol/L (95%CI: -0.04, 0.03).

DISCUSSION

We observed an association between baseline GL and TG and HDL but not LDL at two years follow-up in 8-10-year-old children. Using both the conventional mediation analysis and the MSM with IPW approach to mediation analysis revealed a relationship between GL and TG and HDL that was fully mediated by adiposity.

The ingestion of high GL meals results in a rapid absorption of glucose from the gut that raises blood glucose levels to twice that observed in response to a low GL meal.[34] This hyperglycemic state induces in a rise in insulin levels that persists even after glucose levels have been restored, resulting in a relative hypoglycemic state approximately 4 hours following the meal, and leading to increased hepatic fat synthesis.[34] Consequently, levels of TG and cholesterol esters accumulate in the blood.[35] Population studies in adults have reported indirect associations between high GI and GL diets and high insulin secretion resulting in increased TG[1,2,36] and LDL cholesterol[1] and decreased HDL cholesterol.[2,4,36] However, only two cross-sectional studies have examined the association between GL and the lipid profiles of children and they reported inconsistent results.[5,6]

The effect of dietary GL on adiposity has been shown in clinical trials in adults[37] and in observational studies.[38-41] Meta-analyses have reported a beneficial effect on body weight of low GL diets in overweight and obese children[42] and adults.[43] In addition, the association between adiposity and lipid profiles has been shown in adults and children,[44-50] in intervention and observational studies. Our results are consistent with these findings, showing an association between high dietary GL and adiposity, and between adiposity and higher TG and lower HDL. As well, a meta-analysis assessing the relation between dietary GL and coronary heart disease in adults showed an association that may be more apparent in overweight and obese, suggesting a possible mediation or moderation by obesity.[51] While our analyses did not support an interaction between GL and adiposity, our mediation analysis revealed that the associations between GL and TG and HDL after 2 years were mediated by adiposity. Given that we found partial mediation by adiposity of the association between GL and TG and HDL, we found evidence of alternate pathways. This suggests that dietary glycemic load consumed at 8-10 years of age is associated with unhealthy blood lipids after 2 years, mainly via a pathway that includes adiposity, but also via other pathways. Consequently, in the absence of adiposity, the effect of GL on blood lipids in childhood may be less important but nonetheless present.

When using MSM for causal mediation, there was no evidence of a controlled direct effect. In general, the conventional methods by Baron and Kenny[14] for assessing the direct effect produces an unbiased estimate of controlled direct effect (CDE) only under very specific conditions, and there is a risk of collider stratification bias.[16,17] Although the conventional method fits regression models adjusting for all confounding variables, a spurious associations could be created if the list of confounders includes variables on the pathway from exposure to outcome. For example, an unmeasured confounder of the mediator-outcome association, may lead to collider stratification bias when including the mediating variable in the model.[15] Therefore, MSM with IPW[31] are used to identify controlled direct effects.[17] The main difference between the two mediation analysis methods is that the weighted MSM accounts for confounders between the mediator and the outcome as well as exposure-outcome confounders. The MSM with IPW method also allows for exposure-mediator interactions.[52]

The causal mediation analysis also has limits and specific assumptions that are not always met. For example, the accuracy of the marginal structural model depends on the correct specification of the weight models.[53] In fact, we had to truncate the data to exclude larger weights at the extremities of the data that resulted in unstable estimates. As well, small sample sizes may pose a threat to the positivity assumption.[33,54,55] Specifically, the positivity assumption requires that the probability of treatment be between zero and one, but not zero nor one, for each combination of covariate.[33,54,55] When a sample size is small, and there are several covariates in the weight models, there is a chance that the distribution of treatment will not vary across each covariate combination.[33,54,55] Suggesting that in nutritional studies with small sample sizes, it may be of value to compare results using both approaches to mediation analysis to assess the robustness of findings. In addition, our results from the MSM models yielded slightly smaller effect estimates overall from those obtained with the conventional method, however, given that our confidence intervals for the MSM were wide and overlapped with the confidence intervals from the conventional method, we could not conclude that these effect estimates were different.

Our study has limitations. First, the 24h recall is considered a strong tool for measuring usual dietary intake, particularly when conducted on three or more non-consecutive days, however it may result in measurement error because it relies on memory and recall. The use of disposable containers and a ruler to help with portion estimations and the involvement of the parents at each interview are methods to help decrease recall bias. In addition, interviews were unannounced, and adjustments were made to account for underreporting,[30] which should significantly reduce reporting bias. Second, an important limitation, as previously discussed, is that the causal inference assumptions of consistency, exchangeability and positivity may not be met.[52] As well, the identifiability of the direct effect is dependent on the assumptions of no unmeasured confounding between X and Y, and between M and Y which may also be violated in both the conventional and weighted approach.[52] Third, the QUALITY study only had two timepoints available for analysis, therefore we had to use baseline BMI z-score and percent fat mass as the mediator variables for our mediation analysis. We assumed that the 3 non-consecutive 24-hour recalls represented usual/habitual dietary intake. Finally, the QUALITY cohort was comprised of Caucasian children at risk for obesity, therefore, our results are principally generalizable to those children. As well, while some participants were lost, there were only 10 percent lost to follow-up, therefore we are confident that our results were not significantly affected.

CONCLUSION

In conclusion, our results show that the associations between GL and HDL and TG after 2 years are mediated by adiposity. Disentangling the different components of the association between GL and blood lipids in children is important to accurately target recommendations and interventions. Therefore, interventions to reduce cardiovascular risk factors in children should focus on both decreasing high glycemic load foods and weight management. The marginal structural models with inverse probability weights resulted in more attenuated effect estimates and wider confidence intervals compared to the conventional method, suggesting no difference between the results of both approaches. However, given the size of the sample and potential for violation of the positivity assumption when using weights, the choice of mediation analysis method should be based on the fulfillment of conditions and assumptions of each individual method. In addition, it may be of value to compare results using both approaches to mediation analysis to assess the robustness of findings when applied to nutritional studies.

CONTRIBUTIONS

KS designed the research question for this project, conducted the analysis, interpreted results and wrote the manuscript. AB, MH, KGD and GP participated in the research question design (defining outcomes, identifying confounders, determining appropriate analysis methods), reviewed and edited the manuscript.

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Table 9.1. Population characteristics of children in the QUALITY cohort at baseline and first follow up visit

Characteristic	Baseline n=630	Follow-up n=564
Age (years), mean (SD)	9.6 (0.9)	11.7 (0.9)
Male, %	54.4	55.5
BMI category, %		
Underweight (z-score < -2)	0.3	0.9
Normal weight (z-score ≥ -2 & <1)	56.7	58.3
Overweight (z-score ≥ 1 & < 2)	30.0	28.4
Obese (z-score ≥ 2)	13.0	12.4
Tanner stage, %		
Prepubertal	78.4	33.2
Pubertal	21.6	66.8
Percent fat mass, median (IQR)	25.3 (17.4 to 35.2)	27.8 (19.4 to 36.4)
Screen time, median (IQR), h/d	2.2 (1.3 to 3.7)	2.9 (1.9 to 4.4)
SBP z-score, median (IQR)	-0.79 (-1.26 to -0.35)	-0.85 (-1.37 to -0.39)
DBP z-score, median (IQR)	-1.09 (-1.40 to -0.83)	-1.09 (-1.39 to -0.80)
Triglycerides, median (IQR)	0.7 (0.6 to 1.0)	0.7 (0.5 to 0.9)
HDL cholesterol, median (IQR)	1.2 (1.0 to 1.3)	1.1 (1.0 to 1.3)
LDL cholesterol, median (IQR)	2.3 (2.0 to 2.7)	2.2 (1.9 to 2.6)
Parent education		
no parent with high school diploma	1.4	0.8
1 or 2 parents with high school diploma	6.4	6.4
1 or 2 parents with community college or equivalent	37.8	42.9
1 or 2 parents with university degree	54.4	49.9
Family income, mean (SD)	42,360 (18,574)	48,643 (22,191)
Glycemic index, mean (SD)	52.2 (4.2)	-
Glycemic load, mean (SD)	110.1 (30.8)	-
Carbohydrate intake, mean per day (SD), g	221.3 (56.0)	-
Energy intake, mean per day (SD), kcal	1681.8 (388.4)	-
Sugar-sweetened beverages, median (IQR), ml	67.9 (0.0 to 189.5)	-
Number of snacks, median (IQR)	5 (3 to 6)	-
Physical activity, median (IQR), counts per minute*	559.1 (459.0 to 675.1)	462.3 (374.5 to 587.3)

Abbreviations: SD standard deviation; IQR inter-quartile range

*Accelerometry data only completed for n=535 at baseline and n=418 at follow-up visit

Table 9.2. Total effect and direct effect of glycemic load at baseline on triglycerides after 2 years in children wit
mediator from the QUALITY cohort using regression adjustments and marginal structural model with inverse pr

	Total effect (Regression adjusted[a] for confounders, excluding BMI)	Regression adjusted[a] for confounders and BMI z-score	Mar in
	β (95% CI)	β (95% CI)	
Triglycerides			
Glycemic load[c]	0.06 (0.02, 0.09)	0.04 (0.01, 0.07)	
BMI z-score	-	0.07 (0.02, 0.13)	
LDL cholesterol			
Glycemic load[c]	0.02 (-0.01, 0.05)	-0.02 (-0.06, 0.03)	
BMI z-score	-	0.11 (0.03, 0.18)	
HDL cholesterol			
Glycemic load[c]	-0.02 (-0.04, -0.01)	-0.01 (-0.03, 0.01)	
BMI z-score	-	-0.06 (-0.09, -0.03)	

Abbreviations: Body mass index: BMI, glycemic load: GL, confidence interval: CI

[a] Adjusted for age, sex, tanner stage, screen time, physical activity, family income, parent education, ratio of ener
estimated energy requirement, fat intake (residuals), protein intake (residuals)
[b] Inverse probability weights used to account for potential confounders of exposure-outcome and mediator-outco
Exposure weight model included variables: Age, sex, ratio of energy intake to basal metabolic rate, protein intak
(residual), screen time, season, family income, parent education. Mediator weight model included variables: tann
prepubertal), screen time, fat intake (residual), protein intake (residual), carbohydrate intake (residual), physical a
maternal BMI, paternal BMI, parent education, family income.
[b] Weights truncated at 5-95%
[c] 100-unit increase in glycemic load

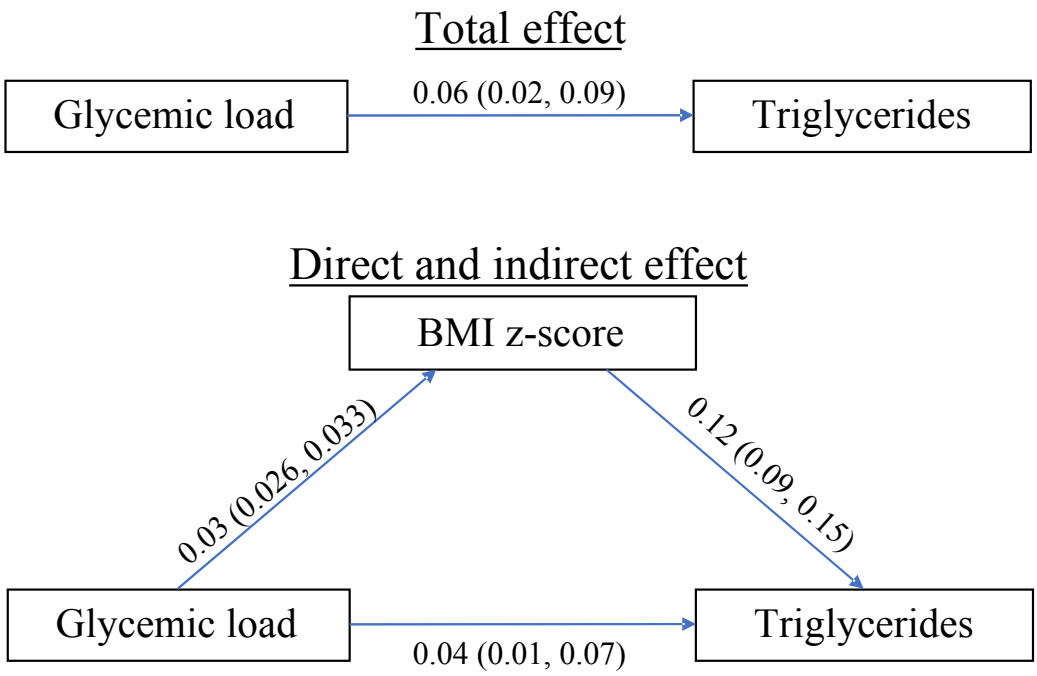
Table 9.3. Total effect and direct effect of glycemic load at baseline on blood lipids after 2 years with percent fat
in children from the QUALITY cohort using regression adjustments and marginal structural model with inverse p

	Total effect (Regression adjusted[a] for confounders, excluding % fat mass)	Regression adjusted[a] for confounders and % fat mass	Margin with in
	β (95% CI)	β (95% CI)	
Triglycerides			
Glycemic load[c]	0.06 (0.02, 0.09)	0.03 (0.003, 0.06)	0.0
Percent fat mass	-	0.01 (0.006, 0.02)	0.0
LDL cholesterol			
Glycemic load[c]	0.02 (-0.01, 0.05)	-0.02 (-0.06, 0.02)	0.0
Percent fat mass	-	0.01 (0.004, 0.02)	0.00
HDL cholesterol			
Glycemic load[c]	-0.02 (-0.04, -0.01)	-0.02 (-0.03, -0.001)	0.0
Percent fat mass	-	-0.005 (-0.008, -0.003)	-0.00

Abbreviations: Glycemic load: GL, confidence interval: CI, high-density lipoprotein: HDL

[a] Adjusted for age, sex, tanner stage, screen time, physical activity, family income, parent education, ratio of ener
estimated energy requirement, fat intake (residuals), protein intake (residuals)
[b] Inverse probability weights used to account for potential confounders of exposure-outcome and mediator-outco
Exposure weight model included variables: Age, sex, ratio of energy intake to basal metabolic rate, protein intake
(residual), screen time, season, family income, parent education. Mediator weight model included variables: tann
prepubertal), screen time, fat intake (residual), protein intake (residual), carbohydrate intake (residual), physical a
maternal BMI, paternal BMI, parent education, family income.
[b] Weights truncated at 5-95%
[c] 100-unit increase in glycemic load

Figure 9.1. Diagram illustrating the total, direct and indirect effects obtained from mediation analysis of glyce cholesterol considering adiposity (BMI z-score) as a mediator (β (95% CI)). Direct effects can be interpreted as f 100-unit increase in glycemic load, β can be interpreted as the unit change in TG cholesterol independent of BM



CHAPTER 10: Summary and Conclusions

10.1. Summary

The objectives of this thesis were 1) to examine characteristics of misreporters of dietary intake within a cohort of children with a parental history of obesity and determine the bias introduced by underreporting, 2) to assess whether glycemic index and glycemic load predict cardiovascular risk factors in children after 2 years of follow-up, 3) to determine the effects of meal-specific glycemic index and load and cumulative effects of high glycemic index and glycemic load on 2-year cardiovascular risk factors in children, and 4) to compare the conventional approach and the causal approach using marginal structural models with inverse probability weights to examine adiposity as a mediator in the association between baseline dietary glycemic load and lipid profile after 2 years. The work in this thesis broadens the available evidence on underreporting in dietary recalls. As well, it furthers knowledge on the role that glycemic index and glycemic load play in obesity and cardiovascular risk factors in children.

Measurement error due to self-report of diet is a major challenge in nutritional epidemiology. The bias that misreporting can induce of the estimation of diet-disease associations has been well documented; however, misreporting remains an issue that is not well addressed in observational nutritional studies. An important step in preventing bias caused by misreporting is to identify potential underreporters in a study and to characterize how they differ from adequate reporters. In this vein, the first manuscript of this thesis showed that underreporters from the QUALITY cohort were generally unhealthy, had higher body mass index, worse cardiometabolic risk factors and low physical activity level compared to adequate reporters. It is not clear why obese individuals tend to underreport more than leaner individuals, but possible explanations include intentionally misreporting actual food intake, possibly due to social desirability or social approval biases, more frequent dieting compared to leaner individuals, or other factors.(141) We also demonstrated the importance of identifying and addressing the bias introduced by underreporters in study results. This is particularly true in individuals that are at a higher risk for obesity because underreporting occurs differentially according to body size. The consequence of not correcting for underreporting includes spurious

associations resulting in incorrect interpretations of results. This manuscript paved the way for analyses conducted in the subsequent manuscripts of this thesis.

In the second manuscript, we showed that glycemic load, but not glycemic index was associated with adiposity and blood lipids in children after 2 years of follow-up. Specifically, glycemic load predicted body mass index z-score, percent fat mass, triglycerides and HDL cholesterol in children after 2 years. The results from this second manuscript emphasize the importance of diet, specifically quality and quantity of carbohydrates in improving cardiovascular risk factors in children.

Consuming a high, compared to a low, glycemic index breakfast may have an effect on the quality and size of subsequent meals. In addition, consuming several high glycemic index meals daily may have long-term effects on obesity and cardiovascular risk. On the other hand, consuming a low glycemic index and load breakfast may help control energy intake during the rest of the day and have long-term benefits on health. In fact, experimental trials have shown that low GI breakfasts lead to increased satiety and lower energy intake during the day particularly in adults and to a lesser extent in children.(142-145) Therefore, we examined the association between meal-specific glycemic index and load and the frequency of high glycemic index and load meals with cardiovascular risk factors in the third manuscript. We discovered that dinnertime glycemic load was slightly associated with increased adiposity and worsened blood lipids after 2 years suggesting that consuming foods high in GL at dinnertime might have the most harmful effect compared to other meals during the day. It should be noted that while the breakfast and lunch GL effect estimates were quite larger than dinnertime GL effects, the confidence intervals of the former were too wide to yield any conclusive results. Nevertheless, our results add to this very limited body of evidence, emphasizing the importance of consuming low GL meals.

The fourth manuscript aimed to compare the conventional approach and the causal approach to mediation analysis to examine adiposity as a mediator in the association between baseline dietary glycemic load and lipid profile after 2 years. We showed that the associations

between glycemic load and HDL cholesterol and triglycerides after 2 years are mediated by adiposity. It is important to be able to disentangle the different components of the association between glycemic load and blood lipids in children in order to accurately target recommendations and interventions. In addition, we illustrated how the two mediation methods yielded similar results. The marginal structural models with inverse probability weights resulted more attenuated effect estimates but wider confidence intervals compared to the conventional method, thus no significant difference between the results of both approaches. However, given the size of the sample and potential for violation of the positivity assumption when using weights, it may be of value to compare results using both approaches to mediation analysis to assess the robustness of findings when applied to nutritional studies.

10.2. Implications for clinical, public health and policy makers

It is well established that cardiovascular risk factors tend to track over time. Worse cardiometabolic risk profiles in childhood, including obesity, atherogenic lipid profile and elevated blood pressure, results in deleterious cardiometabolic profiles in adulthood.(146) The American Academy of Pediatrics recommends prevention of cardiovascular disease by maintaining a healthy weight and normal blood lipid levels in childhood.(147) Nevertheless, childhood obesity remains one of the most important public health issues and its prevalence continues to rise steadily, reaching epidemic levels in certain developed countries.(53, 54) This poses serious public health and social implications including impact on mortality and morbidity, long-term healthcare costs and decreased ability to work. As was stated in a recent editorial by Gardner, the available nutritional research should not be followed-up by additional randomized controlled trials, but should be acknowledged and utilized in public health interventions.(148)

Our results stress the important role of dietary glycemic load in obesity and poor cardiovascular health in children. There is much controversy among nutrition researchers and government health agency on the use of glycemic index and load for dietary recommendations, even within diabetic populations. The American Diabetes Association (ADA) standard of care suggests that the benefits of using glycemic index and load as tool for glycemic control are only

modestly better than focusing on total carbohydrate intake.(149) Additionally, the American Dietetic Association stresses that dietitians must disclose the weak evidence-based effect of glycemic index to their diabetic patients.(150) The ADA's reservations regarding glycemic index and load are based on B level evidence (defined as supporting evidence from well-conducted cohort or case-control studies) and the fact that glycemic index tends to vary greatly within a category of the same food.(149, 150) These reservations are also shared by Health Canada for similar reasons to the ADA, as well as the fact that certain foods that have a low glycemic index are not recommended as part of Canada's Food Guide.(151) Health Canada believes that while the glycemic index is not integrated in Canada's Food Guide, Canadians that follow the Guide will naturally consume a lower overall glycemic index diet . The use glycemic index has shifted with time, going from a tool used solely for diabetic care to a more widespread use in the management and prevention of cardiovascular disease, obesity, certain cancers, in addition to diabetes. Given sufficient experimental and observational research, perhaps the concept of glycemic index or glycemic load might be introduced in public policy guidelines.

While the use of glycemic index as a score is not highly supported for public policy, there is some agreement that rather than focusing on numerical glycemic index and load values of foods, considering the overall "glycemic impact" of foods might be highly relevant.(150) This could be done by providing educational tips for selecting foods from a broad range of nutritious foods within the low glycemic index category to limit the glycemic impact of an individual diet. The benefit of such an approach is that individuals would not be burdened by the need to locate foods with low GI from the over 2400 foods in the International Table of Glycemic Index, which would be doomed to failure.

Randomized controlled trials with fixed dietary interventions ranging from 24 hours to 12 weeks, have consistently shown a beneficial effect of low glycemic load diets on anthropometric measurements, cardiovascular risk factors and metabolic parameters,(10, 152, 153) satiety and decreased energy consumption.(154) Low glycemic index interventions were found to positively affect insulin sensitivity in children with high baseline insulin levels,(155) reduced 24 hour blood pressure measures,(156) and better appetite ratings.(157) However, the general population may

not be capable of adopting the diets from these trials without training and knowledge of the complex glycemic index tables. Integrating the GI into dietary recommendations as lists containing only low glycemic index and load foods might be more effective at attaining ideal body weight and improving cardiovascular risk for individuals. At the population level, policies encouraging a healthy body weight in children through physical activity and diet need be developed. These may include dietary educational tools and interventions aimed at decreasing foods offered to children in schools, summer camps and other settings that have high glycemic index and load.

Given the moderate level of evidence on the effects of high glycemic index and load, policymakers are hesitant to integrate glycemic load in dietary and health recommendations. This emphasizes the need for stronger, more robust, and comparable nutritional epidemiology studies. As per our results in chapter 8, underreporting of energy intake has an important effect on estimation of diet-disease associations in children and methods for identifying underreporting remain inconsistent across studies. In addition, approaches to prevent bias by underreporting also remain controversial. Misreporting is only one of many potential biases in nutritional epidemiology. In a viewpoint published in JAMA, Ioannidis discussed the relevance of nutritional studies to public health, and his views of the low credibility and controversial evidence in the nutrition literature.(158) In order to create a body of highly credible nutrition literature that permits good comparability of results between studies, the development of standardized analysis and bias correction methods is essential.

Our results showed that glycemic load, but not glycemic index, was associated with cardiovascular risk factors in children, and that dinnertime glycemic load in particular had an important impact. It is not clear why glycemic index did not have a similar effect as glycemic load. However, understanding the difference between glycemic index and load can help understand this discrepancy. The glycemic index is defined according to a fixed quantity of specific foods. However, foods are rarely consumed in that specific quantity, resulting in a glycemic index score that is not necessarily representative of the actual glycemic response. On

the other hand, the glycemic load considers the amount of available carbohydrate over and above the glycemic index, thus making this score more representative of the actual glycemic response.

The results obtained in both chapters 9 and 11 emphasize the important role of adiposity in the association between glycemic load and blood lipids. In fact, most of the effect of GL on TG and all of the effect of GL on HDL were mediated by BMI. This stresses the importance of targeting childhood obesity for long-term prevention of cardiovascular disease in adulthood. Obesity is a result of complex interplay of factors which can be divided into environmental and individual factors. Environmental factors include food and activity environment, and social psychology. Individual factors include individual psychology, genetics, physiology and energy balance, which comprises dietary intake and physical activity.(159) Thinking about adiposity as a system comprised of several components is crucial to develop appropriate interventions for prevention and management. In 2015, the Canadian Task Force on Preventive Health Care published new guidelines for the prevention and management of obesity in children and youth.(160) They recommend that structured behavioral, but not pharmacological or surgical, interventions be offered by the general practitioner to promote a healthy weight management. The behavioral interventions should be individually tailored and should include one or any combination of healthy diets, increased physical activity and changes in lifestyle.(160) Our study results suggest that data on glycemic load could inform those recommendations.

10.3. Suggestions for future research

Longitudinal studies of longer duration with additional data collection time points might draw a better picture of the associations studied in this thesis. In addition, we were only able to assess the effect of baseline glycemic load, due to limitations of our data. However, further research should aim to have additional measures of diet over time in order to explore the effect of change in diet. Moreover, given that the QUALITY study only included Caucasian children of European ancestry in order to reduce genetic admixture, further research examining these associations among children of different ethnic backgrounds and within a wider age range would be informative. Future research should also focus on conducting randomized controlled trials

examining the efficacy of a low glycemic load diet intervention in children for potential implementation in schools and settings.

In a recent editorial in the Journal of Clinical Nutrition, Gardner discussed the variation in healthy food contents of individual diets. Within a low glycemic index diet, certain foods that are classified as low glycemic index are not as healthful as others. For example, oatmeal (GL=36) has a much higher glycemic load compared to chocolate milk with sugar (GL=4), however, unlike chocolate milk with sugar, oatmeal contains fiber and vitamins, making it more healthful. Therefore, future research on glycemic index and load could also examine the healthy and unhealthy foods within the realm of glycemic response.

Adiposity, including body mass index and percent fat mass, were identified as important mediators of the association between glycemic load and blood lipids in this thesis. Due to limitations of our data, we did not have a measure of adiposity at a timepoint between the exposure and outcome and we had to assume that baseline dietary data represented past intake. Further research should examine mediation by adiposity with a measure of the mediator obtained at a timepoint after the exposure was measured and before the outcome. In addition, mediation analyses using the causal approach should be conducted among larger sample sizes to ensure that the positivity assumption is met, specifically ensuring that the probability of treatment be between zero and one, but not zero nor one, for each combination of covariate.(139, 161, 162)

10.4. Strengths and limitations

Our study is one of the few studies to assess the longitudinal association of GI and GL on cardiovascular risk factors in children and the first to examine mediation by BMI. The QUALITY cohort data was rigorously collected by highly trained staff and using the most recent measurement tools and provides a large number of covariates. In addition, the QUALITY study carefully considered the advantages and disadvantages of various dietary intake assessment methods and selected the 24-hour diet recalls as the best-suited tool for the 8-10-year-old age group and the main objectives of the study. In the design phase of QUALITY, the team attempted to reduce reporting bias by providing a training session for children and their parents

as well as providing food portion kits and allowing the parents to participate in the interviews. In the design phase, we also assigned glycemic index and load scores following a pre-specified method that was created based on an extensive search of the literature and numerous discussions among investigators to ensure a standardized and precise approach. The assignment of the glycemic index and load scores was done by a single investigator, and reviewed by an expert, to avoid inconsistencies that could arise by the use of numerous research assistants. In the analysis phase, we paid special attention to measurement error by adjusting for underreporting of caloric intake. We also conducted numerous sensitivity analyses to assess the robustness of our results. Despite our efforts to maximize the quality of our studies, certain important limitations remain.

The QUALITY cohort used a school-based sampling strategy to identify potential participants. Caucasian children of Western European ancestry aged 8–10 years with at least one obese biological parent were included. The cohort was restricted to Caucasian families to reduce genetic admixture. Therefore, our results are principally generalizable to Caucasian children at risk of obesity. In addition, the retention rate of the QUALITY study between the first and second visit was 89.5%. Since only eleven percent of children were lost to follow-up, we do not believe that this attrition could have affected our results. However, the group of children lost to follow-up was similar to baseline participants in terms of age and sex but had slightly higher body mass index. While the attrition rate was small, certain variables had missing data, therefore we used multiple imputation techniques to improve our dataset and avoid excluding a large number of participants. We also conducted several sensitivity analyses to assess the robustness of our results for each objective of this thesis.

Although the 24h diet recall is a strong measurement tool in nutritional epidemiology, especially when conducted on three or more non-consecutive days, it can result in measurement error because it relies on memory and recall. However, the use of disposable containers and rulers to help with portion estimations and the involvement of the parents at each interview should reduce recall bias. As well, the fact that interviews were unannounced should considerably reduce reporting bias. In addition, to account for differential reporting, we adjusted for underreporting. When foods consumed at school were obtained from the school cafeteria,

parents did not observe their child's dietary intake at school and could not have participated in the recall for that meal. However, findings from several studies have shown that by the age of 8-10 years children are capable of reporting their food intake during a 24-hour recall as reliably as with the help of their parents, particularly on weekdays.(141, 169, 170) As well, while random error can result from intra-individual variation in intake from day to day, it should be minimized by the use of interviews on three non-consecutive days and averaged across those days. Also, although we adjusted for a variety of dietary and non-dietary confounders, there is still a potential for residual confounding by variables strongly correlated with dietary glycemic index or glycemic load that may also explain or mask an association. This is an inherent limitation of dietary research. However, with the QUALITY data we had access to a wide array of variables making it possible for us to adjust for our complete list of predetermined confounders which should have significantly reduce residual confounding. In addition, there is a potential for residual confounding by non-dietary covariates including sleep patterns and geographic location/neighborhood which can be associated with diet and cardiometabolic health.

Finally, at the time that this thesis was started, the QUALITY cohort had completed only two visits. For this reason, we used baseline body mass index z-score as the mediator for our mediation analysis under the assumption that the three non-consecutive 24-hour recalls represented short-term usual/habitual dietary intake from the near past. In addition, we remain cautious in our causal interpretation of the results of the mediation analysis because the assumptions of consistency, exchangeability and positivity may not have be met.(171) As well, the identifiability of the direct effect is dependent on the assumptions of no unmeasured confounding between exposure and outcome, and between mediator and outcome which may also be violated in both the conventional and weighted approach.(171)

10.5. Conclusions

Through this thesis, we have shown that children who underreport their dietary energy intake have a higher body mass index and worse cardiometabolic risk factors and that addressing underreporting bias in observational studies is important. Furthermore, this thesis highlights the role of dietary glycemic load, as opposed to glycemic index, on cardiovascular risk factors in

children, and the important role that adiposity has as a mediator in these associations. Identifying the role of glycemic load and cardiovascular risk factors adds to current knowledge on the different causes of pediatric obesity and cardiovascular risk factors and provides information to help improve nutritional counselling by dietitians and physicians and potentially also help families make healthy food choices.

CHAPTER 11: References

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APPENDIX 1: McGill ethics approval

McGill

Faculty of Medicine
3655 Promenade Sir William Osler #633
Montreal, QC H3G 1Y6

Faculté de médecine
3655, Promenade Sir William Osler #633
Montréal, QC H3G 1Y6

Fax/Télécopieur: (514) 398-3870
Tél/Tel: (514) 398-3124

August 16, 2019

Dr. Gilles Paradis
Epidemiology, Biostatistics and Occupational Health
1020 Pine Avenue West
Montreal, Quebec H3A 1A2

RE: IRB Study Number A08-M41-19B
The effect of dietary glycemic index and glycemic load on cardiovascular risk factors in school-aged children in Quebec

Dear Dr. Paradis,

Thank you for submitting the above study for IRB review, on behalf of your PhD candidate Karine Suissa.

As this study involves no more than minimal risk, and in accordance with Articles 2.9 and 6.12 of the 2nd Edition of the Canadian Tri-Council Policy Statement of Ethical Conduct for Research Involving Humans (TCPS2 2018) and U.S. Title 45 CFR 46, Section 110 (b), paragraph (1), we are pleased to inform you that an expedited/delegated review and approval for the above-referenced study (March 19, 2015 [sic]) was provided on August 16, 2019. The ethics certificate is valid until **August 2020**. The study proposal will be presented for corroborative approval at the next scheduled meeting of the Institutional Review Board, and a certification document will be issued to you at that time.

A review of all research involving human subjects is required on an annual basis in accord with the date of initial approval. The annual review should be submitted at least one month before **August 2020**. Please inform the IRB promptly of any modifications that may occur to the study over the next twelve months.

Sincerely,

Roberta Palmour

Roberta Palmour, PhD
Chair
Institutional Review Board

cc: Karine Suissa
A08-M41-19B

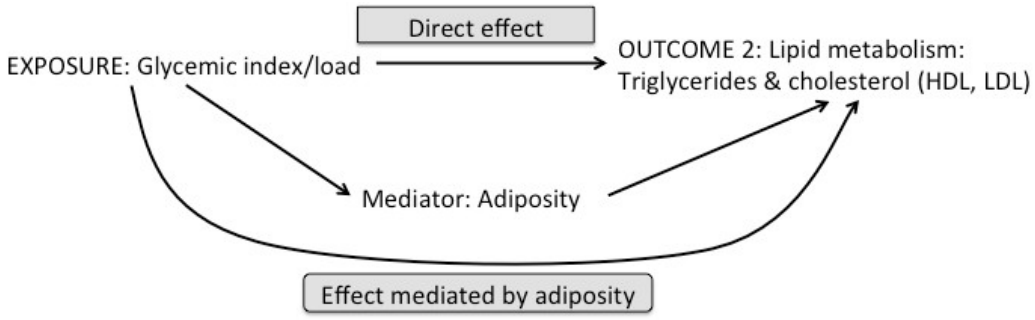
APPENDIX 2: Example of glycemic index and load of common foods

FOOD	GLYCEMIC INDEX	SERVING SIZE	GLYCEMIC LOAD
PEANUTS	14	1⁄4 cup	1
GRAPEFRUIT	25	1/2 large	1.4
KIDNEY BEANS	28	1 cup	7
CHEESE PIZZA	30	2 slices	5.1
SKIM MILK	32	1 cup (8 oz)	4
LOWFAT YOGURT (PLAIN)	33	1 cup	10.2
APPLE, RAW	38	1 medium	6
PEAR, RAW	38	1 medium	4
ALL BRAN CEREAL	38	1 cup	9
SPAGHETTI (WHITE, BOILED 5 MINUTES)	38	1 cup	15
ORANGE, FRESH	48	1 medium	4.4
BANANA, FRESH	52	1 large	12.4
SNICKERS CANDY	55	1 bar	22.1
HONEY	55	1 tbsp	11.9
BROWN RICE (BOILED)	55	1 cup	18
OATMEAL (COOKED)	58	1 cup	11.7
RAISINS	64	2 tbsp	27.3
WHITE RICE (BOILED)	64	1 cup	23
WHITE TABLE SUGAR	68	2 tsp	7
POPCORN (AIR POPPED, PLAIN)	72	2 cups	5.7
WATERMELON	72	2 cups	4.3
WHITE BREAD	73	1 slice	10
DOUGHNUT	86	1 medium	17
RUSSET POTATO	76	1 medium	23
RICE CAKES	78	3 cakes	17
CORN FLAKES	81	1 cup	21
CARROTS, BOILED	92	1/2 cup	3.9

* extracted from the International Table of Glycemic Index (125)

APPENDIX 3: Directed acyclic graph (DAG) for objectives 2 and 4 (mediation analysis)

Figure 1: DAG for the association between GI/ GL and lipid profiles



Exposure-outcome confounders:
- Age
- Sex
- Physical activity
- Parental education
- Household income
- Family history of obesity
- Protein intake
- Fat Intake
- Screen time
- Season
- Ratio of energy intake to basal metabolic rate

Mediator-outcome confounders:
- Age (for % fat mass only)
- Sex (for % fat mass only)
- Tanner stage
- Screen time
- Total energy intake
- Fat, protein, carbohydrate intake
- Physical activity
- Season
- Parental education
- Household income
- Maternal and paternal BMI

APPENDIX 4: Power calculations/ minimal detectable differences

The primary objective of this thesis is to test whether adiposity at follow-up is correlation with baseline GI or GL is the true value of the slope (β) that quantifies this relation. Because the size of the cohort is fixed, I will calculate the minimal detectable differences for the outcomes of interest with a given power and type 1 error.

The general expression that links the test statistic of the type 1 error (Z_α), the test statistic of the power 1- β (Z_β) to the sample size n (=600) assuming a null hypothesis H_0: β=0 vs. H_A: $\beta_{alt}-\beta_{null} = \Delta\beta \neq 0$ is written as:

$$Z_\alpha * SE_{null}\beta + Z_\beta * SE_{alt}\beta * Z_\beta = \Delta\beta$$

If we can assume that the SE is the same under the null and alternative hypotheses, the formula for n can be written as:

$$n = (Z_\alpha + Z_\beta)_2 * (SD_{y2} / [SD_{x2} * \Delta\beta_2])$$

We can reorder the formula to isolate $\Delta\beta_2$. Using the n=600, α=0.05, and β=0.2 (for a power of 0.8), we can then calculate the minimal detectable slope $\Delta\beta$.

$$\Delta\beta = \sqrt{(7.84 * SD_{y2}) / (600 * SD_{x2})}$$

by plugging in SDs for x and y obtained from the QUALITY cohort and the literature we can obtain minimal detectable differences for each outcome

Variable x	**SD_x**
GI	2.7
GL	40.4
Variable y	**SD_y**
%BF	6.8
BMI	4.3
TG	0.45
HDL	0.25
LDL	0.66
SBP	13.6
DBP	7.5

The minimal detectable differences obtained for each exposure-outcome pair are show in the following table and figure:

X	SDx	Y	SDy	$\Delta\beta_2$	$\Delta\beta$
GI	2.7	%BF	6.8	0.0829	0.288
GI	2.7	BMI	4.3	0.0331	0.182
GI	2.7	TG	0.45	0.0004	0.019
GI	2.7	HDL	0.25	0.0001	0.011
GI	2.7	LDL	0.66	0.0008	0.028
GI	2.7	SBP	13.6	0.3315	0.576
GI	2.7	DBP	7.5	0.1008	0.318
X	**SDx**	**Y**	**SDy**	$\Delta\beta_2$	$\Delta\beta$
GL	40.4	%BF	6.8	0.0004	0.019
GL	40.4	BMI	4.3	0.0001	0.012
GL	40.4	TG	0.45	0.0000	0.001
GL	40.4	HDL	0.25	0.0000	0.001
GL	40.4	LDL	0.66	0.0000	0.002
GL	40.4	SBP	13.6	0.0015	0.038
GL	40.4	DBP	7.5	0.0005	0.021