COW'S MILK FAT AND CHILD GROWTH, DEVELOPMENT AND NUTRITION

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ABSTRACT

Background: Health Canada and the Canadian Paediatric Society suggest that children over age 2 years transition from whole (3.25%) to reduced fat (0.1-2%) milk in effort to lower dietary fat intake and reduce the risk of overweight and obesity. However, observational studies have demonstrated that higher milk fat intake is associated with lower child adiposity. The optimal milk fat for child growth, development and nutrition is unknown.

Objectives: 1) Determine the relationship between milk fat and child adiposity among existing literature, 2) Understand parent and physician perspectives about milk fat for children, 3) Evaluate the relationship between milk fat and child zBMI among children aged 9 months-8 years in the TARGet Kids! cohort, and 4) Design and launch a randomized controlled trial (RCT) to determine the effect of recommendations for whole vs. reduced fat milk on zBMI among children aged 2-4 years.

Methods: 1) A systematic review and meta-analysis was conducted, 2) A qualitative study which sought to understand current practice, attitudes and preferences about milk fat for children aged 2-5 years, 3) A prospective cohort study was conducted using linear mixed effects models, and 4) A RCT protocol (Cow's Milk Fat Obesity pRevention Trial or CoMFORT) was developed to be embedded in TARGet Kids!.

Results: Among 20,897 children aged 9 months-18 years, those who consumed whole milk had 0.61 (95% CI 0.52-0.72, p< 0.0001) the odds of overweight or obesity compared to reduced (0.1-2%) fat milk. Parents provide, and physicians recommend different cow's milks for children, and hold mixed interpretations of the role of milk fat in children's diets. Within TARGet Kids!, children (N= 7467) aged 9 months-8 years who consumed whole milk had 0.84 the odds of overweight (95% CI 0.77 to 0.91, p< 0.0001) and 0.82 the odds of obesity (95% CI 0.68 to 1.00, p= 0.047) compared reduced fat milk. The CoMFORT trial was launched in February 2020 and has recruited 8 participants to date.

Conclusion: Evidence supports that children who consume whole milk have lower risk of overweight or obesity. This information will guide future research and recommendations and policies for children's nutrition.

ACKNOWLEDGMENTS

My experience of completing a PhD began with a mistake in my application where I forgot to delete a joke I had included, stating “I look forward to becoming a science guru.” Whether the admissions committee didn’t notice, didn’t care, or found this to be the substance of a U of T doctoral student I’ll never know, but in any case, I thank them for their oversight.

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LIST OF ABBREVIATIONS

25(OH)D	25-hydroxyvitamin D
AAP	American Academy of Pediatrics
AI	Adequate Intake
ALA	Alpha-Linolenic Acid
AMDR	Acceptable Macronutrient Distribution Range
aOR	Adjusted Odds Ratio
BMI	Body Mass Index
CCHS	Canadian Community Health Survey
CCK	Cholecystokinin
CDC	Centers for Disease Control
CER	Comparative Effectiveness Research
CFG	Canada's Food Guide
CHD	Coronary Heart Disease
CHMS	Canadian Health Measures Survey
CI	Confidence Interval
CINAHL	Cumulative Index to Nursing and Allied Health Literature
CLA	Conjugated Linoleic Acid
CoMFORT	Cow's Milk Fat Obesity pRevention Trial
CPS	Canadian Pediatric Society
CRP	C-Reactive Protein
CrI	Credible Interval
DHA	Docosahexaenoic Acid
DRI	Dietary Reference Intake
EAR	Estimated Average Requirement
EMBASE	Excerpta Medica Database
FE	Fixed Effects
FFQ	Food Frequency Questionnaire
GI	Glycemic Index
GIP	Glucose-dependent Insulinotropic Peptide
GLP-1	Glucagon-Like Peptide-1
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HDL	High-Density Lipoprotein
HEI	Healthy Eating Index
HOMA-IR	Homeostatic Model Assessment of Insulin Resistance
HR	Hazard Ratio
ICT	Innovative Clinical Trial
IL-1β	Interleukin-1 Beta
IL-6	Interleukin-6

IP-TFA	Industrially-Produced Trans Fatty Acid
IOM	Institute of Medicine
IOTF	International Obesity Task Force
IU	International Units
LA	Linoleic Acid
LDL	Low-Density Lipoprotein
MeSH	Medical Subject Heading
NHANES	National Health and Nutritional Examination Survey
nmol/L	Nanomols per litre
NOS	Newcastle Ottawa Scale
NR	Not Reported
OB	Obesity
OW	Overweight
OR	Odds Ratio
OW/OB	Overweight or Obesity
PREMs	Patient-Reported Experience Measures
PTH	Parathyroid Hormone
PUFA	Polyunsaturated Fatty Acid
RE	Random Effects
RCT	Randomized Controlled Trial
RDA	Recommended Dietary Allowance
RP-TFA	Ruminant-Produced Trans Fatty Acid
RR	Risk Ratio
SES	Socio-Economic Status
SFA	Saturated Fatty Acid
SPOR	Strategy for Patient Oriented Research
SSB	Sugar-sweetened Beverage
TARGet Kids	The Applied Research Group for Kids
TNF-alpha	Tumor Necrosis Factor-alpha
TwiCs	Trials within Cohorts
UL	Tolerable Upper Level
WC	Waist Circumference
WHO	World Health Organization
WIC	Women, Infants and Children
zBMI	Body Mass Index z-score

STUDENT CONTRIBUTIONS

- Wrote thesis including 4 peer reviewed manuscripts; co-authored 4 additional manuscripts: 2 about patient oriented research in TARGet Kids!, 1 validation paper about beverage consumption measurement in TARGet Kids!, 1 letter to the editor
- Received A+ in all courses taken
- Developed protocol for systematic review and meta-analysis, screened and selected studies, analyzed and described results of included studies
- Developed questionnaire and interview scripts for qualitative study, collected data through online questionnaires and in-person interviews, transcribed and analyzed transcripts
- Designed prospective cohort study, conducted statistical analysis
- Assisted with conceptualization, protocol development and grant applications for CoMFORT, SOY/SMILE, NuRISH, PACT, HiCARE, COVID-19 in Children and Families
- Secured REB approval for CoMFORT and qualitative study
- Trained research assistants for CoMFORT protocol
- Obtained buy-in from TARGet Kids! physicians for CoMFORT
- Launched CoMFORT in TARGet Kids! clinics and coordinated REDCap logistics
- Developed PACT including operationalizing and facilitating meetings, liaising with members
- Gave 1000 presentations
- Awarded 1st place at St. Michael's Hospital Elevator Pitch Competition for *Cow's milk fat: which is best for children?*
- Awarded People's Choice Award at the University of Toronto 3-Minute Thesis Competition for *Cow's milk fat: which is best for children?*
- Attended and presented research at Canadian Pediatric Society, Pediatric Academic Societies, SPOR Summit, TwiCs Symposium conferences
- Mentored peer lab members Erika Gibson, Laura Elliott, Izabela Soczynska, Curtis D'Hollander, Sepi Mortazavi, Queenie Zhang
- Starred in CIHR Talks video
- TAed for Basic Human Nutrition, Nutrition Literacy and Chronic Disease
- Guest lectured for NFS284 Basic Human Nutrition: Lipids Metabolism
- Took McMaster Health Forum Patient-Oriented Research Masterclass

CHAPTER 1: INTRODUCTION

Childhood obesity has increased fivefold in the past 40 years with nearly 1 in 3 Canadian children now living with overweight or obesity.[1] Children who are overweight or obese are at increased risk for a variety of cardiometabolic and mental health complications, such as type 2 diabetes, anxiety and depression.[2] Cow's milk has long been a childhood dietary staple, and an inexpensive and convenient source of protein, carbohydrate, fat and micronutrients such as vitamin D and calcium. Since 1992, Health Canada, the National Institutes of Health, the Canadian Paediatric Society (CPS) and the American Academy of Pediatrics (AAP) have recommended that children 2 years of age and older consume reduced fat milk (2% or 1% fat) to limit dietary fat and prevent childhood obesity.[3] However, this recommendation is consensus-based and has a low GRADE (Grading of Recommendations Assessment, Development and Evaluation) level of evidence to support it. Observational data from my Master's thesis[4] and other evidence[5-11] has suggested that consuming reduced fat milk during early childhood is associated with childhood overweight and obesity. Although the biological mechanism underlying this relationship remains unclear, a growing body of evidence has challenged the assumption that dietary fat contributes to excess adiposity in children.[12-14] Further, dietary fat from whole cow's milk may have other benefits such promoting vitamin D absorption leading to higher vitamin D stores.[4] According to the American Academy of Family Physicians, "although the use of lower-fat milk is probably safe in the second year of life and is effective in reducing total fat intake, the evidence has yet to show its overall benefit."[15] It is unclear whether switching from whole milk to reduced fat milk at age 2 years is appropriate or beneficial.

To our knowledge, no clinical trials have evaluated the relationship between cow's milk fat and childhood adiposity. Several observational studies have identified a paradoxical relationship between higher milk fat consumption and lower childhood overweight and obesity. My cross-sectional study in 2016 involving 2745 *TARGet Kids!* children aged 1-5 years indicated that children who consumed whole (3.25% fat) milk had a lower body mass index z-score (zBMI), an age- and sex-adjusted measure of child adiposity, relative to children who consumed 1% milk (0.72 units lower zBMI).[16] Other large studies of children have reported similar findings. A study involving 852 children from Boston found that higher intake of whole milk at 2 years of age was associated with lower BMI at 3 years (0.09 unit lower zBMI per daily serving, 95% CI -0.16 to -0.01).[17] A study of 1467 Italian children age 3-11 years found that whole cow's milk was associated with lower zBMI while reduced fat milk was not.[18] A longitudinal study of 10,700 American children from the Early Childhood Longitudinal Survey Birth Cohort found that children who consumed reduced fat milk (vs. whole milk) at 2 years of age had increased odds of being overweight or obese (OR=1.57, 95% CI 1.03 to 2.42) at 4 years of age.[19]

One theory underlying the relationship between cow's milk fat and excess adiposity is the displacement of calories from less healthy foods such as sugar sweetened beverages (SSBs).[20] Whole milk may induce satiety through the release of hormones such as cholecystokinin, reducing desire for other foods.[21] Alternatively, fatty acids found in cow's milk such as trans-palmitoleic acid and conjugated linoleic acid may be metabolically protective. Higher circulating levels of trans-palmitoleic acid have been associated with lower adiposity, insulin resistance, triglycerides, and incidence of type 2 diabetes, and positively associated with HDL cholesterol in several large adult cohort studies.[22-26] Randomized controlled trial (RCT) evidence suggests that conjugated linoleic acid supplementation for overweight and obese children is effective in reducing body fat.[27] Vitamin D, which is lower among children who consume reduced fat milk as well as children with higher adiposity, may also play a role.[28-36] Low circulating vitamin D may impair lipolysis,[37] beta cell function and glucose sensitivity.[38] Though parents may choose milk with a fat content to counter-balance the adiposity of their child (i.e. higher fat milk for a leaner child and vice versa), little evidence exists to support this relationship.[39]

Given that nearly all children in North America consume cow's milk daily, determining which milk fat optimizes children's growth, development and micronutrient status is urgently needed. The purpose of this doctoral thesis was to create high quality evidence about the relationship between cow's milk fat and excess adiposity in childhood. Using a step-wise approach, four studies have been included in this thesis: 1) A systematic review and meta-analysis which synthesized the available evidence on cow's milk fat and child adiposity; 2) A qualitative study to understand parent and clinician perceptions and attitudes about cow's milk fat for children; 3) A prospective cohort study to evaluate the longitudinal relationship between cow's milk fat and child adiposity from age 9 months to 8 years of age; and 4) A protocol for a randomized controlled trial called CoMFORT (Cow's Milk Fat Obesity pRevention Trial) evaluating the effect of recommendations for whole vs. reduced fat cow's milk between ages 2-4 years on child zBMI at age 4 years. Collectively, the first three projects provided the justification and informed the design of the CoMFORT study. Overall, this research adds to the body of evidence that describes the relationship between dietary intake of cow's milk fat and overweight or obesity in early childhood.

The literature review (Chapter 2) is divided into four sections: cow's milk, childhood adiposity, the relationship between cow's milk and child health, and patient-oriented research methods. Chapters 3, 4, and 5 expand on the following studies: 1) *Whole vs. reduced fat cow's milk and child overweight: a systematic review and meta-analysis*; 2) *Qualitative study to understand parent and physician perspectives about cow's milk fat for children;* and *3) Cow's* *milk fat and child adiposity: A prospective cohort study*. Finally, the clinical trial protocol which has been informed by this work is included in Chapter 6: *Cow's Milk Fat Obesity pRevention Trial (CoMFORT): A primary care embedded randomized controlled trial to determine the effect of cow's milk fat on child adiposity*. A general review and discussion of the thesis results can be found in Chapter 7.

CHAPTER 2: LITERATURE REVIEW

2.1 Cow's milk

2.1.1 History

Cow's milk has been consumed by humans for 10,000 years, originating in present-day Europe and Africa.[40] It is generally understood that the introduction of dairy farming and cow's milk production for European and African diets led to an increase in the human ability to sustain lactase production beyond infancy. Lactase is an enzyme that breaks down lactose, which is a carbohydrate found in cow's milk.[40] Most humans possess lactase in their gastrointestinal tract at birth to aid in the digestion of breastmilk, which also contains lactose.[41] It is assumed that continued stimulation to produce lactase by the introduction of cow's milk into the diet caused a shift in human biology called lactase persistence.[42] Lactase persistence allows the body to produce lactase and tolerate milk throughout the life course, rather than only during breastfeeding. Today, lactase persistence is still rooted in European and African regions, but is present in about one third of all humans.[42] Some regions in Asia do not share the agricultural history of dairy farming, and therefore lactase persistence is less frequent.[43] Nonetheless, cow's milk is consumed by people of a variety of ages, ethnicities and from varying geographic locations around the world.[41]

While it is unclear why cow's milk became integrated into human farming practices, diets, and digestive abilities,[44] it is speculated that the effects of breastmilk on infant nutrition were desirable beyond weaning from the breast.[41,45] Without awareness of its exact nutritional composition, it was likely that cow's milk promoted children's growth and was therefore believed to contain important nutrients.[42] In modern times, it is now known that cow's milk contains carbohydrates, protein, fat, and a variety of vitamins and minerals which support children's growth except vitamin C, iron and fibre. A single food matched for quantity and breadth of nutrients to cow's milk is rare beyond highly fortified industrial food products. Cow's milk is a convenient vehicle for providing the nutrition that growing children need, and smooths the transition from breastmilk or infant formula to other foods consumed during childhood and beyond. Modern agriculture has developed and sustained ways to produce and distribute cow's milk widely. Advancements in technology have allowed for safe and consistent production of a product that people enjoy. For these reasons, cow's milk has succeeded as a dietary staple for many generations and cultures.

2.1.2 Canadian guidelines for milk and dairy consumption

Canadian agricultural techniques were influenced by European practices;[46] hence, cow's milk has long been a part of the diets of Canadians who predominantly migrated from Europe. In 1923, the Division of Child Welfare in Canada published the *Canadian Mothers Book,* which provided advice for maternal and child health at a time when food was becoming produced more for consumption en masse as opposed to home farmed, grown and prepared.[47] At this time, regulations were in place to ensure the safety and cleanliness through pasteurization of widely distributed cow's milk. Recommendations in Canada were largely based on expert opinion and industry suggestions:

> *"Milk is the indispensable food for children. They cannot do without it. The cow has been well called the ''the foster mother of the human race.'' Little children must have milk to enable them to grow properly. No matter what it costs, milk is still the cheapest food for children. Children from nine months to two years should have about two pints of milk every day in addition to other food, and it is really a mistake to give them any less till they are about twelve years of age. Three large cups of milk a day is the very least they should have (Department of Health, 1923, p. 107)."*[47]

The first set of Canada Food Rules in 1942 recommended children to start consuming cow's milk at 9 months and consume at least one pint of milk (473 mL) per day. This is consistent with current guidelines. The prescribed amount of milk suggested for various age groups of children varied with each iteration of Canada's Food Rules and Guides since then. Even when food was rationed during war time, children were still recommended to maintain milk consumption. In 1949, children and adolescents were recommended to drink 2 cups (473 mL) and 3 cups (710 mL) of milk per day, respectively. By 1961, adolescents were encouraged to drink 1000 mL of milk per day. In 1977, milk recommendations expanded to include other dairy foods upon the introduction of four "food groups." Children were advised to consume 2-3 servings of milk and milk products daily, defined as 3 of: 1-250 mL cup of milk, 1.5 ounces of cheese, or ¾ cup of yogurt. Canada's Food Guide to Healthy Eating in 1992 was the first to suggest for children, "choose lower fat milk products more often." This continued in the 2007 version, which advised children and adolescents to "drink skim, 1%, or 2% milk each day." Children aged 2-8 years were now recommended 2 servings of milk and alternatives per day; children aged 9-18 years 3-4 servings.[48] The 2019 Canada's Food Guide recommends that all Canadians should make water their "drink of choice," but also lists "white, unsweetened lower fat milk" as a healthy drink choice.[49]

Canada's Food Guide has never made explicit recommendations for children younger than two years of age. Health Canada has made nutrition recommendations for infants through a document titled "Nutrition for Healthy Term Infants: Recommendations from 6-24 Months."[50] These guidelines recommend introducing whole (3.25%) cow's milk at 9-12 months of age and not to exceed 750 mL of milk per day. At age 24 months, children are referred to general guidelines for healthy eating (i.e. Canada's Food Guide) which recommend reduced fat milk (generally defined as 0.1-2% fat). Recommendations from Health Canada, the Canadian Paediatric Society and Dietitians of Canada match these recommendations but suggest that children younger than 5 years of age refrain from skim (0.1% fat) milk.[50,51] These guidelines are found in the Rourke Baby Record, which is a standardized tool used by primary healthcare providers across the country.[52]

2.1.3 International guidelines for milk consumption

Various health agencies recommend that whole fat (3.25%) milk be started between 9 and 12 months of age, depending on developmental milestones.[53] In the United Kingdom, Europe, and Australia, similar dietary guidelines exist from the National Health Service (UK),[54] World Health Organization (Europe),[55] and Government of Australia.[56] Specific European guidelines vary by country, but most emphasize reduced fat dairy products for maintaining a healthy diet.[57] The American Academy of Pediatrics (AAP)[53] and National Institutes of Health (NIH)[3] state that children younger than 2 years should only receive whole (3.25% fat) milk to ensure adequate calorie intake for proper growth and development.[53] Older children, however, may switch to 2%, 1% or skim to help achieve a low fat diet, as "diets high in fat may contribute to heart disease, obesity, and other health problems later in life."[3] The recommended quantities are 2-250 mL cups per day for children age 2-8 years, and 3 cups daily for children aged 9-18 years.[53] The American Academy of Family Physicians (AAFP) outlined a number of nutrition guidelines for toddlers aged 1 to 4 years and has assigned each an evidence score from "A" (highest) to "D" (lowest). Recommendations for 2-3 servings of milk per day and limiting dietary fat and cholesterol for children both received a "C" rating. Further, the AAFP stated, "although the use of lower-fat milk is probably safe in the second year of life and is effective in reducing total fat intake, the evidence has yet to show its overall benefit."[15]

2.1.4 Cow's milk consumption in children

Based on 2004 Canadian Community Health Survey (CCHS) data, 88% of Canadian children aged 1-3 years had consumed milk on the previous day; older children (ages 4-8) were slightly less likely to drink milk, with 80% of boys and 71% of girls reporting consumption.[58] Canadian Community Health Survey data from 2015 (cycle 2.2) indicated that children aged 2 to 8 years typically consumed 3 servings of milk or dairy products per day; older children aged 9 to 18 years typically consumed about 2 servings daily despite higher daily serving recommendations from Health Canada at that time.[59,60] According to the WHO, at age 12 months, about one third of Canadian children's dietary energy intake is estimated to come from either breastmilk or cow's milk, or both.[61]

In Canada, whole milk sales declined from 1,022,379 kilolitres per year in 1977 to 355,307 kilolitres in 2015. At the same time, skim (0.1%), 1% and 2% sales rose from 1,226,324 kilolitres in 1977 to 1,942,347 kilolitres in 2015. Per capita, 72.8 litres of whole milk were consumed per person in 1960, compared with 10.1 litres per person in 2015. Peak consumption of reduced fat milk occurred in 2000 at 17.3 litres per person; in 2015, this had fell to 14 litres per person.[62]

National Health and Nutrition Evaluation Survey (NHANES) data showed that between 2005 and 2010 in the USA, females aged 4-8 years were estimated to consume an average of 279 mL of milk per day, while on average, males were estimated to consume an average of 312 mL of milk per day. Children in this survey aged 2-18 years derived an average of 10-15% of their daily energy intake from cow's milk.[63] Updated NHANES data from 2005-2012 indicated that 63% of children aged 12-24 months consumed whole cow's milk daily and 25% consumed reduced fat (2%, 1% or skim).[64] Children aged 12-24 months who consumed whole milk had a mean intake of 572 g per day, whereas the mean reduced fat milk intake was estimated to be 446 g per day.[64] Among children aged 4-13 years in the USA, cow's milk was the leading source of energy from beverages in 2010.[65] Between 2009 and 2014, only 17.8% of children aged 4-19 participating in NHANES reported consuming cow's milk as their main beverage compared with 13.5% who consumed a mix of milk and juice, 5.6% only juice, or 63.2% other caloric beverages. Children who chose cow's milk most often consumed an average of 511 g per day and derived 15.3% of their daily energy from cow's milk.[66] Overall cow's milk consumption in American children under 5 years of age decreased by 7% from 1976-2006;[67] during the same period the proportion of pre-adolescent children who did not consume milk doubled from 12% to 24%.[68]

In Australia, a 2007 survey of children aged 2 to 16 years (N= 4487) revealed that 28% of children regularly consumed unflavoured cow's milk, and these children had an average intake of 376 g per day.[69] A prospective cohort study of younger children in Australia showed that cow's milk was consumed often; 91% of 2 year old children (N= 515) consumed milk and alternatives daily which contributed to an estimated 22% of children's daily dietary energy intake. Eighty-six percent of 3 year old children (N= 426) consumed milk daily, which contributed an estimated 12% of daily energy intake, and 77% of 5 year olds (N= 405) consumed milk which contributed to 9% of daily energy intake.[70]

In the UK, nationally representative survey data indicated that whole milk consumption among children aged 1.5-4.5 years decreased from 82% of children in 1992 to 69% in 2009, and among children aged 4-19 years, the proportion who consumed whole milk decreased from 44% to 30%. Reduced fat cow's milk consumption rose in both groups over the same period, and overall energy intake from cow's milk among all surveyed children decreased.[71]

Little nationally representative data from other countries with similar dietary practices, guidelines, and food availability as Canada is available. It should also be noted that measurements of children's dietary intake are often completed by a proxy (ie., parent) and are subject to biases such as recall bias, where the true amount or variety of food is misremembered, social desirability bias, where a perceived "better" food is reported than the one consumed, and measurement bias, where instruments used to capture dietary intake do not account for types of foods actually consumed.[72]

2.1.5 Predictors of cow's milk consumption in children

A number of factors have been identified which are associated with the likelihood of a child consuming cow's milk. The most influential predictor of cow's milk consumption worldwide is child age. Younger children are more frequent consumers of milk, and consume it in larger quantities than older children. Data suggest a transition from cow's milk to sugar-containing beverages as children get older.[66,73,74] Males tend to consume more milk than females,[75] possibly due to higher average energy needs, or social factors such as perceived need to feed boys more than girls.[76] Children who consume milk are more likely to have parents who are older, non-Hispanic, and consume milk regularly themselves, according to one American study.[77] Children of non-European ethnicity both in Canada and the United States tend to consume less milk than children of European descent.[58,78] While whole milk is slightly more expensive than reduced fat milk (approximately $0.25 more per litre), lower socioeconomic status has not been found to be a strong predictor of reduced fat cow's milk consumption.[75,79] To the contrary, families with lower income have been shown to be more likely to purchase higher fat cow's milk for children.[80] Lower-income families who receive support from food stamps or WIC (Women, Infants and Children) programs in the United States may purchase more cow's milk than other low socio-economic status (SES) families who do not receive such support.[81] However, families with children over age 2 years who are receiving WIC support are only eligible to receive financial support to purchase 1% milk.[82] Availability of cow's milk in school lunch and breakfast programs also positively predict cow's milk consumption in children.[75]

A systematic review of educational interventions to increase cow's milk consumption among preschool aged children identified 14 interventions. Characteristics associated with successful interventions included being located in a single setting (for example, a preschool), targeting a specific behaviour change (altering the environment and prompting changes in routines), and involving both the parent and child. Overall, only 35% of identified educational interventions showed evidence of an increase in dairy consumption among children, indicating that targeting factors such as access, cost or availability of preferred products may be necessary for successful interventions.[83]

2.1.5.1 Nutrient composition of cow's milk

Human breast milk is regarded as the nutritional gold standard for infants because of its macronutrient, micronutrient and immunological properties.[84] Specifically, it is considered a complete source of nutrition, defined as containing all of the nutrients needed to support human growth (one exception is vitamin D).[85] Cow's milk has a similar macronutrient distribution: approximately 50% of calories from carbohydrates, 30% from fat, and 20% from protein.[86] Nutrition facts tables for skim, 1%, 2%, and whole cow's milk are shown in Table 1.[87]

Cow's milk produces distinct metabolic and glycemic responses when consumed by humans. When consumed with food, milk has been shown to result in lower blood glucose and better appetite suppression following a meal rich in carbohydrates compared to other beverages, including water.[88-90] Though cow's milk proteins are thought to be largely responsible for these observations, the type and quantity of the other macronutrients found in cow's milk may play a role in this response.[91] Cow's milk is known to trigger the release of a number of hormones, such as glucagon-like peptide 1 (GLP-1), cholecystokinin, (CCK), and peptide tyrosine tyrosine (TYY), which influence glycemia and appetite.[91-93] A study by Panahi et al. determined that when the carbohydrate, fat and protein components of whole cow's milk are consumed independently, their effects on glycemia, hormonal response, and gastric emptying are less pronounced than when consumed together suggesting synergistic effects.[94]

Table 1. Nutrition facts tables for (left to right) skim, 1%, 2%, and whole milks.[87]

Nutrition Facts / Valeur nutritive — Per 1 cup (250 mL) / pour 1 tasse (250 mL) — Amount / Teneur	Skim	% Daily Value / % valeur quotidienne	1%	% Daily Value / % valeur quotidienne	2%	% Daily Value / % valeur quotidienne	Whole	% Daily Value / % valeur quotidienne
Calories / Calories	90		110		130		160	
Fat / Lipides	0 g	0 %	2.5 g	4 %	5 g	8 %	8 g	13 %
Saturated / saturés	0 g	0 %	1.5 g	8 %	3 g	16 %	5 g	26 %
+ Trans / trans	0 g		0 g		0.1 g		0.2 g	
Cholesterol / Cholestérol	5 mg		10 mg		20 mg		30 mg	
Sodium / Sodium	125 mg	5 %	120 mg	5 %	120 mg	5 %	125 mg	5 %
Carbohydrate / Glucides	13 g	4 %	12 g	4 %	12 g	4 %	12 g	4 %
Fibre / Fibres	0 g	0 %	0 g	0 %	0 g	0 %	0 g	0 %
Sugars / Sucres	13 g		12 g		12 g		12 g	
Protein / Protéines	9 g		9 g		9 g		9 g	
Vitamin A / Vitamine A		10 %		10 %		10 %		10 %
Vitamin C / Vitamine C		0 %		0 %		0 %		0 %
Calcium / Calcium		30 %		30 %		30 %		30 %
Iron / Fer		0 %		0 %		0 %		0 %
Vitamin D / Vitamine D		45 %		45 %		45 %		45 %

2.1.5.1.1 Lactose

The primary carbohydrate in cow's milk (4.5 g per 100 mL) is lactose, which is a disaccharide composed of glucose and galactose. Lactose is synthesized in the mammary gland by the combination of glucose with uridine diphosphate galactose. Alpha-lactalbumin is the protein enzyme responsible for catalyzing this reaction, and is also found in cow's milk. In order to digest lactose, the enzyme lactase is required in the intestinal tract of the consumer. Lactase breaks lactose down into its monomers, glucose and galactose, which are then absorbed through the villi of the jejunum.[95] From there, the sugars are transported to the liver through the portal vein.[96]

Lactose is a unique carbohydrate because its glycemic index (GI), or ability to raise blood glucose relative to pure glucose,[97] is relatively low (46). Although the energy density of lactose is the same as other carbohydrates (4 kcal per gram), it is digested at varied levels of completeness because of varied levels of lactase between people. The combined effect is a relatively slow rise in blood sugar following cow's milk consumption.[96]

Bacterial fermentation of lactose in the colon may reduce the energy contribution of non-absorbed lactose by 1-2 kcal per gram.[96] Lactose may act as a prebiotic, or source of nutrition to bacteria in the intestine, and its fermentation produces short chain fatty acids which can be absorbed to some extent.[96] Lactic acid-producing bacteria (which use lactose for energy) can exhibit beneficial effects on gut health and potentially play protective roles against Crohn's disease and ulcerative colitis.[98] Fermented lactose in the colon also aids in the absorption of calcium and magnesium, which are present in cow's milk.[96,99]

2.1.5.1.2 Protein

Milk proteins are primarily composed of casein (82%) and whey (18%). Cow's milk provides 3.2 g of protein per 100 mL. Both casein and whey are considered high quality proteins based on their bioavailability, amino acid completeness (i.e., they contain all of the amino acids which are essential for human metabolism), and digestibility. Cow's milk protein has a protein digestibility corrected amino acid score of 1.0, which refers to the proportion of essential amino acids provided by a food after digestion.[100] As milk proteins are digested, bioactive peptides are released, which play a variety of roles, including antiviral, antifungal, antioxidant, antihypertensive, antithrombotic and immunomodulatory.[101]

Whey proteins in cow's milk include β-Lactglobulin (β-LG), α-Lactalbumin (α-LA), serum albumin, immunoglobulins, lactoferrin and proteose-peptone fractions.[92] Relative to casein, whey protein is quickly digested, but digestion and absorption of amino acids in the intestine is slow relative to other proteins.[92] Whey protein consumption is associated with lower food intake after ingestion compared to casein, soy, or egg proteins,[102] but the mechanism is not fully known.[92] Whey protein is especially rich in branched-chain amino acids (BCAA; including leucine, isoleucine, valine and lysine), which play an important role in muscle anabolism[103] and insulin secretion.[104] Though various nutrients elicit digestive hormone release, whey protein intake has been shown to stimulate the release of CCK and GLP-1, satiety hormones known to increase the feeling of fullness in humans.[105-108] CCK delays gastric emptying, and sends signals to the brain to reduce food intake, promoting satiety.[109-111] GLP-1 is known to reduce gastrointestinal motility and gastric emptying,[112] contributing to the "ileal brake" which is the inhibition of gastrointestinal transit and release of gastric and digestive secretions.[113] Finally, whey protein has been shown to suppress ghrelin, an appetite stimulating hormone, and subsequently reduce food intake in humans.[106]

Whey peptides aid in micronutrient absorption; for example, lactoferrin supports iron absorption and beta-lactoglobulin is a retinol carrier.[114] β-LG and α-LA contribute to angiotensin converting enzyme (ACE)-inhibitory peptides, which have favourable effects on blood pressure and inflammation.[115,116] Whey protein has been shown to reduce inflammatory cytokines IL-6 and interleukin-1 beta (IL-1β).[117] Together, these effects may mitigate cardiometabolic risk factors.[92]

Casein proteins are classified as either α1-casein, α2-casein, β-casein or ϰ-casein, which contribute to binding, transport and improving the digestibility of minerals, specifically for calcium and phosphorous.[100,101] Casein exists in a micelle in cow's milk, which when denatured by stomach acid causes it to form a "clot" in the stomach.[100] This clotting allows casein to delay gastric emptying and slowly release amino acids into the bloodstream over time, elongating satiety.[118]

Insulin-like growth factor-1 (IGF-1) is a notable peptide in cow's milk. Bovine and human IGF-1 are molecularly the same.[119] Although IGF-1 is also endogenously produced in humans, children who consume more cow's milk tend to have higher levels of circulating IGF-1 compared to children who consume less cow's milk.[45,120,121] Circulating IGF-1 has also been shown to be higher after cow's milk consumption.[122] Casein appears to be a trigger in either the release of IGF-1 in cow's milk consumers, or hepatic production of IGF-1, but the exact mechanism is not yet known.[41,45] Cow's milk consumption and circulating IGF-1 levels also do not always correlate linearly. For example, adults do not exhibit the same response as children:[123] throughout the life course, IGF-1 levels in the blood tend to be highest during periods of growth, and are lower in malnourished individuals.[124] IGF-1 promotes skeletal growth;[125] it facilitates calcium and phosphate metabolism and contributes to bone integrity and development.[126]

2.1.5.1.3 Fat

Dairy fats are composed in the following approximate distribution: 65-70% saturated, 25-30% monounsaturated, 2-5% polyunsaturated, and about 3% trans fat. Whole cow's milk contains 3.25 g of fat per 100 mL, on average. Cow's milk fat is highly complex, containing over 400 distinct fatty acids which are mostly (98%) triacylglycerol, and diacylglycerol, cholesterol, free fatty acids, and phospholipids, which together make up the remaining 2% of milk fats.[127] Common fatty acids found in cow's milk are listed in Table 2. The fat content and composition of milk tends to vary with animal feed, season, stage of lactation and ruminal fermentation.[101,127]

For example, the difference in proportion of saturated fatty acids in grain-fed vs. grass-fed cow's milk has been observed to be 39.4% vs. 54.1%, respectively.[128]

Table 2. Common fatty acids found in a sample of Swedish cow's milk.[127]

Fatty acid	**Weighted mean %**
Saturated fatty acids total	*69.4*
4:0 butyric acid	4.4
6:0 caproic acid	2.4
8:0 caprylic acid	1.4
10:0 capric acid	2.7
12:0 lauric acid	3.3
14:0 myristic acid	10.9
15:0 pentadecanoic acid	0.9
16:0 palmitic acid	30.6
17:0 heptadecanoic acid	0.4
18:0 stearic acid	12.2
20:0 arachidic acid	0.2
Mono-unsaturated fatty acids, cis, total	*25.0*
10:1 decenoic acid	0.3
14:1 myristoleic acid	0.8
16:1 palmitoleic acid	1.0
17:1 cis-10 heptadecanoic acid	0.1
18:1 oleic acid	22.8
18:2 linoleic acid	1.6
18:3 alpha-linolenic acid	0.7
Trans fatty acids total	*2.7*
16:1t trans-palmitoleic acid	0.4
18:1t trans-vaccenic acid	2.1
18:2t trans-linoleic acid	0.2
CLA conjugated linoleic acid	0.4

Fat droplets in cow's milk are enveloped by a milk fat globule membrane (MFGM), which is composed of polar lipids and proteins in a 1:1 ratio by weight.[129] The lipid portion contains phospholipids and sphingolipids, which include phosphatidylcholine and sphingomyelin, and cholesterol.[129] The protein fraction is composed of a wide variety of proteins, including enzymes, immunoglobulins, and transporters.[130] The membrane is responsible for preserving individuality of milk fat droplets; mechanical processes such as churning can disrupt the MFGM to create solid milk fat products (i.e., butter).[131] These globule membranes are not digestible by pancreatic enzymes in the small intestine. Several health benefits of the MFGM have been suggested, attributed to cholesterol-lowering, vitamin-binding, and anti-microbial properties.[131] In breast milk, the MFGM is suggested to be a factor that differentiates growth and developmental discrepancies between breast- and formula-fed infants, such as cognitive development.[132] Choline, a compound found in phosphatidylcholine and sphingomyelin, is functionally similar to folate and contributes to neural development and neurocognitive health.[132,133] Bovine MFGM supplementation in infancy may be associated with higher cognitive development scores according to RCT evidence.[134,135] In one clinical trial, 120 infants aged <2 months at baseline were randomized to receive either MFGM-enriched fortified infant formula, or standard fortified infant formula until age 6 months to determine if incidence of diarrhea would decrease. An additional 80 infants received breast milk. A secondary outcome was cognitive development according to the Bayley Scales of Infant and Toddler Development. At 12 months of age, there was evidence that children who received the MFGM formula had higher cognitive scores (105.8 ± 9.2 vs. 101.8 ± 8.0; $p= 0.008$), and similar scores to the infants who received breast milk.[135] However, future research with primary cognitive outcomes is needed.

In adults, there is evidence to support that MFGM supplementation to foods containing saturated fats may reduce intestinal cholesterol absorption. In a crossover RCT of 34 men and women, participants received 45 g/day of buttermilk, which is naturally rich in MGFM, and a micro- and macronutrient matched placebo control for 4 weeks each. There was evidence that the buttermilk intervention led to a reduction in serum cholesterol (-3.1%, $p= 0.019$), LDL cholesterol (-3.1%, $p= 0.057$) and triglycerides (-10.7%, $p= 0.007$) compared to placebo among participants.[136] Other evidence suggests MFGM supplementation may improve inflammatory profiles and post-prandial insulin responses in adults.[137]

2.1.5.1.3.1 Saturated fatty acids

Saturated fatty acids are included in structures and molecules involved in cell signaling, metabolism, inflammation, and transcription.[138] Dietary intake of saturated fatty acids (SFAs) are known to result in higher levels of circulating low-density lipoprotein (LDL) cholesterol[139,140] and the development of cardiovascular disease.[140] Intake of certain SFAs raises total (LDL and HDL) cholesterol when compared to carbohydrates and unsaturated fatty acids.[141]

The relationship between SFA intake in isolation and morbidity and mortality is a thoroughly debated and ongoing issue.[142] Some recent evidence supports a hypothesis that saturated fat may not independently predict reduced cardiovascular health.[24] A meta-analysis by de Souza et al. examined the association between dietary saturated fat, which is present in fat-containing dairy products, and all-cause mortality, cardiovascular disease, type 2 diabetes, or stroke in 12 prospective cohort studies involving 339,090 participants.[24] There was no evidence of an association between saturated fat intake and all-cause mortality, cardiovascular disease mortality, total coronary heart disease, ischemic stroke, or type 2 diabetes. However, the certainty of these conclusions was reported as "very low" according to GRADE and substantial heterogeneity between studies was observed ($I^2 > 60\%$[143] with $p < 0.05$ in most analyses).[24] A meta-analysis conducted by Chowdhury et al. revealed similar findings, which included 49 observational studies of 538,141 participants and 27 RCTs of 105,085 participants. In this meta-analysis, dietary intake of saturated fatty acids was not associated with coronary heart disease (RR= 1.03; 95% CI 0.98 to 1.07, p value not reported), and dairy-sourced saturated fatty acids were negatively associated with coronary heart disease.[144] In one prospective cohort study of

5029 adults, saturated fat sourced only from dairy was associated with a lower risk of cardiovascular disease (HR= 0.79 per 5 g of dairy SFA intake per day, 95% CI 0.68 to 0.92, $p < 0.01$).[145] As far as we are aware, no study has analyzed the relationship between childhood saturated fat intake from dairy or other foods and morbidity or mortality in later life.

Different types of saturated fatty acids may have different effects on human health.[146,147] Given that there are 35 different saturated fatty acids[148] which are consumed in an infinite number of permutations of intakes of these fats based on the types and quantities of foods consumed by individuals worldwide and various lifestyle factors that may all influence outcomes, broad statements about singular nutrients in isolation are challenging to interpret.[138] Saturated fatty acids are believed to have different effects on cardiovascular health depending on their source and structure.[149] For example, odd-chained (carbon chains in odd-numbered quantity) SFAs may be protective[150] whereas others may raise serum lipid and cholesterol levels.[151] A prospective cohort study of 125,287 adults from 18 countries conducted over 10 years revealed that saturated fat intake was associated with higher concentrations of total and LDL cholesterol, but also higher concentration of HDL cholesterol and lower circulating triglycerides. Furthermore, this study revealed that replacing saturated fats with simple carbohydrates was associated with the most adverse serum lipid and cholesterol levels, adding complexity to the current understanding of health effects of dietary fat.[151]

The saturated fatty acids found in cow's milk mainly include palmitic, oleic, and stearic, which make up about 65-70% of total bovine fatty acids.[152] Functionally, these fatty acids are important in the structure and integrity of cell membranes.[147] There is evidence to suggest there may be a relationship between palmitic acid intake and higher circulating IL-6 and white adipose tissue,[153] which have been positively associated with inflammation and obesity, though most of this evidence is limited to animal studies or small-scale human studies.[154] Epidemiological studies and those comparing palmitic acid to other sources of fats, including unsaturated fats, have not demonstrated clear differences in cardiovascular or glycemic health outcomes.[155,156] Oleic acid is widespread in the diet and can be synthesized endogenously. Similar to polyunsaturated fatty acids, oleic acid reduces the oxidation potential of LDL cholesterol, which is a pro-atherosclerotic process.[157] Oleic acid may also have protective effects on inflammation, blood glucose, insulin resistance, and high blood pressure, though actual effects are likely modest.[147] Stearic acid (denoted as 18:0) accounts for 5-15% of cow's milk fat,[158] and is the least efficiently metabolized saturated fatty acid in milk; due to the structure of stearic acid, its absorption is interrupted and postprandial fatty acid response can be delayed or lowered.[159,160] Stearic acid is considered a long-chain SFA and contributes to the structure and function of gangliosides.[147] Stearic acid is often studied as an oil supplement consisting of shea or cocoa butter, or a hydrogenated synthetic oil. A meta-analysis of 35 clinical trials of healthy adult subjects revealed that stearic acid, when compared to other fats such as lauric, palmitic, and trans fatty acids, tended to lower circulating LDL cholesterol levels. In fact, stearic acid's cholesterol-lowering effects have been found to be similar to those of polyunsaturated oleic and linoleic acids.[158] Current evidence is unclear as to the thrombotic[161] and glycemic effects[162] of stearic acid. Further research is needed to understand the cardiovascular, thrombotic, and glycemic effects of stearic acid contained within cow's milk, and broadly, to distinguish the effects of saturated fatty acids found in dairy compared to other dietary sources.

There has been considerable debate about the relationship between specific dietary fats and human health because of the difference between highly controlled trials of individual, prescribed fatty acids and real world diets, which represent "complex matrices of nutrients, minerals, bioactives, food structures, and other factors (e.g., phospholipids, prebiotics, probiotics) with correspondingly complex effects on health and disease."[163] Several investigators have argued that results of highly controlled trials on fatty acids be interpreted with caution, and that when it comes to dairy, the whole dairy food must be considered rather than the sum of its constituents in relation to health outcomes.[158,164,165] Observational sources of evidence about saturated fat intake and health are also subject to scrutiny, as dietary measurements in observational research may be biased[166] (*see 2.1.4*), and residual confounding is possible where diets high in saturated fat may be associated with factors such as lower physical activity, smoking and higher alcohol consumption and sub-optimal social determinants of health.[167,168]

2.1.5.1.3.2 Other fatty acids

Linoleic acid (an omega-6 fatty acid) and α-linoleic acid (an omega-3 fatty acid) are unsaturated fatty acids found in low concentrations in cow's milk. Though found in low concentrations in cow's milk, these fatty acids exist in a ratio (2:1 for linoleic to alpha-linolenic, as compared to some foods which may provide a ratio of 10:1) that is considered beneficial because it allows polyunstaturated fatty acids (PUFAs) to endogenously convert to long-chain PUFAs, such as docosahexaenoic acid (DHA). This ratio may be important for children due to the integral role long-chain PUFAs may have on cognitive and retinal development.[169,170]

Trans-fatty acids (TFAs) include trans-palmitoleic acid, vaccenic acid and conjugated linoleic acid.[127] Intake of industrially produced trans fatty acids, such as those found in hydrogenized vegetable oils, have been associated with lower HDL and higher LDL concentrations in the blood, as well as higher risk of coronary heart disease.[171] The mechanisms driving these relationships may be pro-inflammatory and endothelial deregulatory properties which promote adipose accumulation and insulin resistance, creating a unique "cardiometabolic imprint" of TFAs.[172] It is also possible that the adverse outcomes noted in the many observational studies are due to low incomes, limited food choices, over-reliance on heavily advertised foods and mental health issues rather than specific nutrients; to know for sure, high quality RCTs are needed.

Ruminant-produced trans fatty acids (RP-TFA) are a different class of TFAs and may have different effects on human health. Ruminant-produced trans fatty acids comprise approximately 4-6% of all fatty acids in cow's milk,[173] but quantities are subject to variation due to season, bovine feeding practices (i.e. grain vs. grass fed), and geography.[174] Unlike industrially produced trans fatty acids, RP-TFA are produced by bacteria in the rumen of cows. Some of the polyunsaturated fatty acids ingested by cows are metabolized into RP-TFA, and are passed into tissue and milk. The relationships usually observed between trans fatty acid intake and poor health outcomes are not typically observed with RP-TFA intake.[175] In fact, RP-TFA intake has been associated with lower risk of coronary heart disease.[176,177] It is possible that structural differences contribute to this distinction, but evidence for this is inconclusive.[172]

Conjugated linoleic acid (CLA) is a RP-TFA made from fermented linoleic and α-linoleic acid in the rumen.[101] Several animal and few human studies have evaluated the possible protective health effects of dietary CLA. CLA has demonstrated a number of beneficial properties, such as supporting the immune system,[178] as well as lowering LDL cholesterol[179] and fat mass[180,181] through increased lipolysis and increased energy expenditure leading to lower fat accumulation in animals.[182,183] Human trials show that CLA supplementation can lower overall[184,185] and abdominal fat mass,[178] including over a sustained period (24 months) of weight loss and maintenance.[180] A meta-analysis of 15 RCTs that observed the effects of CLA supplementation for 6 months or more on body composition in overweight and obese adults revealed that on average, CLA supplementation reduced body weight by 1.33 kg (95% CI -1.79 to -0.86, p value not reported).[186] In children, an RCT of 3 g/day CLA supplementation vs. placebo resulted in lower body fatness in 6-10 year olds over 7 months. Plasma lipids and glucose were not changed by the intervention.[27] However, not all trials of CLA supplementation delivered through dairy products have not provided evidence for lower body weight.[187,188] Future studies of usual quantities (130-440 mg/day)[189] of CLA in children would improve understanding of a realistic role of CLA in metabolic health.

Dietary vaccenic acid, a ruminant-produced trans fatty acid, is largely derived from incompletely hydrogenated PUFAs in ruminants such as cows. Vaccenic acid is a precursor to CLA through desaturation in both ruminants and humans, which may allow it to contribute to beneficial effects of CLA once metabolized.[190]

Higher circulating levels of trans-palmitoleic acid have been associated with lower adiposity, incident diabetes, insulin resistance, and triglycerides, and positively associated with HDL cholesterol in several large adult cohort studies; however, these findings could be due to something else since they are from observational studies.[22-26] Vaccenic acid also is a precursor to trans-palmitoleic acid in humans, which may contribute to the positive correlation between dairy fat intake and circulating trans-palmitoleate concentrations in the blood.[191] Though the exact mechanisms for these relationships are unknown, dietary trans-palmitoleic acid is hypothesized to suppress hepatic fat production for energy storage.[159]

Butyric acid is one of few short-chain fatty acids found in cow's milk, and is known for providing energy to gut microflora and moderating inflammation in the digestive tract.[192] Though only shown in mouse studies, there is some evidence to suggest that butyric acid may have beneficial effects on body weight and metabolism.[193,194]

2.1.5.1.4 Biomarkers of dairy fat intake

Common phospholipid biomarkers for dairy fat intake are serum pentadecanoic acid (15:0) and heptadecanoic acid (17:0) because they are ruminant-produced fatty acids excreted in cow's milk.[149,195] Higher concentrations of these fatty acids in the blood have been associated with lower cardiometabolic risk factors including fasting glucose[196], insulin resistance,[197] diabetes,[198] ischemic heart disease,[199] heart attack[196,197,200] and stroke.[201] Multiple studies have identified that individuals with higher dairy fat intake had higher circulating pentadecanoic acid (15:0), which also was associated with lower risk of coronary heart and cardiovascular diseases, as well as lower circulating triglycerides and blood pressure.[202] Though pentadecanoic acid is not relatively abundant in cow's milk, dairy is its main dietary source, and small changes in serum concentrations may be meaningful, or a proxy for another bioactive molecule.[202]

2.1.5.1.5 Vitamins and minerals

Cow's milk provides a variety of micronutrients. Table 3 shows the Health Canada recommendations for intakes of nutrients found in cow's milk, and the quantity a child can obtain from the recommended 2 cups of cow's milk per day.

Table 3. Health Canada micronutrient recommendations for a 1-3 year old child and provision from 2 cups of cow's milk.[203,204]

Nutrient	RDA	Quantity in 500 mL whole cow's milk	Percent contribution
Vitamin A	700 IU (RAE)	790 IU (RAE)	113%
Vitamin D	400 IU	248 IU	62%
Vitamin B_6	0.5 mg	0.18 mg	36%
Vitamin B_{12}	0.9 mcg	2.2 mcg	244%
Thiamin	0.5 mg	0.22 mg	44%
Riboflavin	0.5 mg	915 mcg	1830%
Folate	150 mcg (DFE)	25 mcg (DFE)	17%
Calcium	700 mg	550 mg	79%
Potassium	3000 mg	644 mg	21%

Phosphorous	460 mg	410 mg	89%
Magnesium	80 mg	50 mg	63%
Zinc	3 mg	2 mg	67%

Minerals such as calcium, potassium, zinc, and phosphorous are prominent in cow's milk.[205] One serving of cow's milk provides approximately 30% of an individual's recommended daily allowance (RDA) for calcium.[87] Though less bioavailable than other food sources of calcium, cow's milk delivers the highest quantity of calcium per serving or usually consumed amount of various foods.[206] Phosphorous, another prominent mineral found in cow's milk, works with calcium to promote hydroxyapatite strength.[207] An estimated one third of children's dietary intake of phosphorous comes from dairy products.[208,209] Children who consume more cow's milk are more likely to meet their daily requirements for magnesium, which is important for muscle and nerve function.[210,211] Iodine is not consistently found in high quantities in cow's milk and can depend on season, geography and type of cattle feed, but studies have shown that children who consume more dairy receive more dietary iodine,[212] possibly due to the use of iodine on cow udders for sterilization.[213] Zinc is known to benefit immune response in people who are zinc deficient and is a component of insulin. Zinc intake has been documented to be higher in children who consume more cow's milk than others,[214] as well as higher serum zinc and copper concentrations among milk drinkers.[215] According to the Continuing Survey of Food Intakes by Individuals in the United States, dairy products were the most influential dietary source of potassium in children aged 2-17 years.[211]

Cow's milk is a source of vitamins A and D, both of which are fat soluble. The fat contained in cow's milk may aid the absorption of these vitamins, even in skim (0.1% fat milk).[216,217] Cow's milk is the main dietary source of vitamin D among North American children.[58,218,219] The Canadian Food Inspection Agency standardized fortification at 32 to 52

IU/100 mL fluid milk, or approximately 100 IU per 250-mL cup.[220] In a number of analyses, dairy foods were the most substantial source of vitamin A in children due to similar fortification laws in many countries.[208,209] In Canada, vitamin A is added to cow's milk at 141 to 293 IU/100 mL, or 543 IU per 250-mL cup.[220] Vitamin A is biologically active when found in animal-derived foods, making cow's milk an excellent source due to its vitamin A quantity and quality. Vitamin A is important for the development of immune, reproductive and visual systems, and is therefore very important during childhood.[221] Naturally occurring vitamins in milk include thiamin, riboflavin, pantothenic acid, folate, vitamin B_6 and vitamin B_{12}, which are important for nutrient metabolism, and neural development and integrity. Like many other micronutrients, milk and dairy product consumption is a robust predictor of meeting daily recommended intake levels of these nutrients.[211,222,223] In particular, vitamin B_{12} is only found in animal-sourced foods and vitamin B_6 is mainly animal derived, making dairy foods an especially convenient vehicle for vitamin delivery.[223] Though rich in many nutrients, cow's milk lacks iron which is a key nutrient for child growth and cognitive development.[50]

2.1.6 Effects of cow's milk consumption during childhood

Cow's milk provides children with macro- and micronutrients that are similar to breast milk. It provides a convenient, easily accessible and generally well-tolerated source of fluid nutrition during the transition away from breastmilk or infant formula.[224] In Canada, milk is a highly regulated food with little variation between farm or distributor and carries a low risk of microbiological contamination.[225]

Carbohydrates are the body's most readily available source of energy for daily activities, brain function, and growth. Carbohydrates are the predominant nutrient in breast milk by weight, suggesting an important role in early growth and development.[84] Throughout childhood, carbohydrates support essential processes such as providing energy to the brain, muscle and red blood cells.[226]

Fat is an essential part of a child's diet, contributing to energy storage for constant growth and activity, as well as brain development.[227] Fat also aids in the absorption of fat-soluble vitamins[227] and provides energy through oxidation in the liver. Fatty acids are also used to build cell membranes, as signaling molecules including hormones, and for regulation of transcription factors.[147] During infancy, the brain requires polyunsaturated omega-3 fats to develop and create myelin sheaths responsible for nerve signal transmission as well as support retinal development, and this need for fat continues throughout childhood.[227]

Higher dietary saturated fat and cholesterol intake in childhood has raised concern about increasing the risk of cardiovascular disease later in life. Since cow's milk is often the main dietary contributor to saturated fat and cholesterol in childhood,[228,229] a few studies have evaluated effects of saturated fat from cow's milk and cholesterol in children. A recent cross sectional study from the TARGet Kids! group identified that 2-8 year old children had 0.024 mmol/L higher serum non-HDL cholesterol concentration per 1% higher cow's milk fat consumed. However, children who consumed higher cow's milk fat were not at higher odds for high serum cholesterol concentration (>3.75 mmol/L).[230] A randomized controlled trial of 1062 infants aged 7-13 months assigned participants to either dietary counseling to maintain dietary fat <30% total energy, consume monounsaturated, polyunsaturated, and saturated fat in equal quantities, and consume <200 mg cholesterol per day, or an unrestricted diet. Participants who received counseling were advised to consume skim (0.1%) milk, whereas unrestricted participants were advised to consume at least 1.9% fat cow's milk. Results showed that participants who received counseling consumed less saturated fat, energy, and more PUFAs than those in the control group. Boys (but not girls) had lower serum cholesterol concentrations (-0.39 mmol/L, 95% CI -0.52 to -0.26 among boys; -0.15, 95% CI -0.29 to 0), but similar growth to children in the control group with higher intakes of saturated fat and energy, and lower intakes of PUFAs in the control group.[231] A longitudinal study of preschool children aged 24-70 months revealed that there was evidence of an association between dietary fat intake and body fat %, but when the analysis was restricted to dietary fat from dairy sources only, there was no evidence of an association.[232] Another prospective cohort study revealed that children with the highest intakes of dairy during preschool, who also had the highest saturated fat intakes, had the lowest anthropometry measurements (body fat %, skinfold thickness, and BMI) during later childhood, up to age 13 years. Though this analysis did not pinpoint the sources of total and saturated fat, authors suggest that dairy consumption was a predominant source of dietary saturated fat.[233]

Cow's milk is also a predominant source of dietary protein for children. NHANES 2003-2006 data show that children aged 2-18 years consumed 13.2% of their dietary protein from cow's milk.[234] A prospective cohort study of 203 German children aged 6 months to 6 years revealed that age 18-24 months was the period during childhood when children consumed the highest proportion of energy (13.8%) from protein. Further, children at that age sourced 41% of their dietary protein from dairy.[235] During childhood, protein supplies amino acids for growth of the organs, muscles and skin. Whey and casein proteins play unique roles in the body; for example, whey proteins constitute immunoglobulins[205] and casein is a factor in micelle formation, which are responsible for transporting nutrients and other molecules throughout the body.[236] Minimum protein requirements for children are often exceeded through dietary intake of cow's milk and meats, both of which are encouraged for children who are transitioning from breast milk or infant formula to solid food.[237] It is not uncommon for children to consume 3-4 times their daily requirement for protein.[235,238,239] Further research is needed to understand if dairy protein has different effects on body composition than other sources of protein in childhood, and if there are periods of childhood when susceptibility to negative effects of high protein intake may be more pronounced than others.[193]

Cow's milk is the main dietary source of vitamin D for most children, but not all children who consume cow's milk are vitamin D replete.[240] According to Maguire et al., each daily cup of cow's milk consumed was associated with a higher serum 25-hydroxyvitamin D level of about 4 nmol/L (95% CI 2.5 to 5 nmol/L, $p < 0.001$) among children aged 2-5 years.[218] Among other studies of low vitamin D levels in children, not consuming cow's milk is a common contributing factor.[241-243] Vitamin D deficiency in toddlers was less likely among those who consumed cow's milk than non-milk drinkers in a study by Gordon et al. in 2008 in the United States.[241,242] Children who consume non-cow's milk beverages may be exposed to fewer dietary sources of vitamin D since not all non-cow's milks are fortified with vitamin D and these "milks" may not be consumed as routinely as cow's milk, therefore these children may be at a higher risk for vitamin D insufficiency.[244,245]

Several review articles have summarized articles which describe relationships between cow's milk consumption and various health outcomes during childhood. Key findings are found in *Appendix 8.2: Table 1*. Systematic reviews have identified that cow's milk in children's diets was positively associated with child height,[246] dental,[223] and bone health.[223,246,247] Systematic reviews on the relationship between total dairy consumption and child adiposity have had conflicting findings, though.

Research about cow's milk consumption, body composition and adiposity is described in Section 2.9.1.

2.1.6.1 Bone health and height

Several randomized controlled trials and observational studies have identified a positive relationship between cow's milk intake and bone mineral content in children.[214,248,249] For example, a randomized controlled trial of 12 year old Chinese girls (N= 82) showed that an average 300 mL higher daily cow's milk intake increased bone mineral content (27.0% vs. 24.1%, p= 0.009) over 18 weeks.[120] However, it is unclear whether higher bone mineral content results in lower fracture risk, or lower risk of bone disease later in life, though there is some observational evidence to show cow's milk may be protective against both outcomes.[250,251] Active nutrients likely include protein, calcium, vitamin D, phosphorous and potassium, all of which are involved in bone turnover, structure and integrity.[252] It is likely that the importance of milk as a supplier of these nutrients is highest during periods of growth, especially when bones are being mineralized and more susceptible to fracture.[223] Whey protein has also been suggested to support bone formation, but further evidence is needed.[253]

Consumption of non-cow's "milk" beverages has been associated with lower circulating vitamin D levels[244] and lower height in children in observational studies,[254] which may indicate poorer bone health among children who substitute other beverages for cow's milk. It has been identified that children who did not consume cow's milk were more likely to experience bone fracture,[250,255,256] insufficient circulating concentrations of calcium and vitamin D,[257] which are needed for bone growth and integrity,[257] and lower bone mineral density.[250] More evidence about non-cow's "milk" beverages in children's diets is needed.

Bone health is associated with height during childhood; bones require the same nutrients to both elongate and gain strength and integrity.[45] Various studies have identified a positive relationship between cow's milk intake and height in children.[79,258,259] This relationship is hypothesized to be reliant on a number of vitamins and minerals such as calcium, vitamin D, phosphorous and potassium, but also insulin-like growth factor 1 and cow's milk proteins, which are contributors to longitudinal growth.[45] A meta-analysis of 12 randomized and non-randomized controlled trials from around the world evaluating the relationship between cow's milk intake and child height (age 2-18 years) revealed a linear relationship that each additional 245 mL cup of cow's milk per day was associated with 0.4 cm taller height.[246]

2.1.6.2 Cognitive development

Cow's milk contains many nutrients known to support brain development in early life and cognition throughout the life course. Though the relationship between milk and mental function has not been studied extensively, a systematic review of 8 studies (cross-sectional and prospective cohort ranging from 3-30 years of follow up) on the topic showed that poorer cognitive function in adults was associated with lower cow's milk intake, but this protection may only be offered by reduced fat dairy[260] and could be due to residual confounding. If valid, the observed health benefits of cow's milk consumption could be related directly or indirectly to the brain. For example, better vascular health and lower inflammation could offer protection against both chronic cardiovascular and metabolic diseases, but also cognitive decline.[261,262] On the other hand, nutrients found in cow's milk may be driving these relationships, such as calcium or protein. A 65-year observational follow-up study of children revealed that cow's milk consumption during childhood was associated with better balance and walking times in adulthood, which are markers of cognitive function. However, higher calcium and protein intakes were also positively associated with these outcomes[263] and these findings could be due to other factors such as social determinants of health and physical activity.

The developing human brain requires fat for optimal development and function.[15,264] The human brain is predominantly composed of fat, suggesting that fat is likely an important contributor to brain development and performance.[265] Most of brain growth is completed by age 6 years.[266] Though it has been suggested that milk fat globules contained in breastmilk are beneficial to the growing brain,[132] less attention has been focused on dietary fat and brain development and performance post-infancy, and no clinical trials that we are aware of have assessed the effect of cow's milk fat content on children's brain development. Dietary fat restriction in childhood may impact cognitive development as this period is a time of rapid growth, causing the central nervous system to be susceptible to negative environmental influence.[267] The ratio of essential fatty acids linoleic to alpha-linolenic acid (n-6 to n-3) in whole cow's milk is known to optimize circulating DHA,[268] which is an essential fatty acid to brain growth and function.[269]

2.1.6.3 Cardiometabolic health

Cardiometabolic risk refers to an individual's probability of cardiovascular disease, type 2 diabetes, or stroke. Though risk factors for cardiometabolic diseases may include age, ethnicity, family history or other unmodifiable factors, research with cardiometabolic risk outcomes usually focuses on modifiable factors such as circulating triglyceride or cholesterol concentrations, blood pressure, or body weight or fatness.[270] Cardiometabolic risk factors also include physical activity level, sleep, and diet quality, but in this section "cardiometabolic risk factors" will be referred to as physical manifestations of risk.

It is known that plaque buildup in blood vessels leading to atherosclerosis originates in early life,[227] and that early life cardiovascular disease risk factors are positively associated with cardiovascular events during adulthood.[271] Certain conditions such as hypertension, hyperlipidemia and overweight are known to track from childhood to adulthood. Lifestyle factors such as low physical activity, poor diet, excess energy intake and smoking can exacerbate the development of cardiovascular disease.[272,273] However, the exact causes of early atherosclerosis such as arterial fatty streaks, elevated blood pressure, and elevated total and LDL cholesterol concentrations are not known, and interventions to mitigate children's cardiovascular risk factors have not shown to be consistently effective.[274] Further, some children who exhibit early evidence of atherosclerosis such as fatty streaks cease to exhibit them in adolescence or adulthood,[275,276] highlighting a need for further study of the development of cardiovascular disease over the life course. Evidence is limited on the relationship between cow's milk intake and cardiometabolic health during childhood. However, cow's milk consumption has been evaluated in relation to various cardiometabolic outcomes in many adult populations worldwide. In general, systematic reviews have identified that higher cow's milk consumption has not been associated with higher modifiable cardiometabolic risk factors, or cardiovascular outcomes such as heart attack, stroke or mortality.[193,277-279] Higher cow's milk intake has been associated with lower risk of cardiovascular disease in adult prospective cohort studies (follow up range 5-25 years),[277] and elevated blood pressure in adult prospective cohort studies (follow up 2-15 years),[280,281] regardless of fat content. For example, in a large prospective cohort study[282] involving 136,384 adults aged 35-70 from 21 countries, individuals who consumed only whole fat dairy (>2 servings per day of milk, yogurt or cheese) had lower risk of total mortality (HR= 0.75, p = 0.015), and major cardiovascular disease (HR= 0.68, p = 0.0001) compared to those who consumed <0.5 servings per day after adjusting for age, sex, education, urban or rural location, smoking status, physical activity, history of diabetes, family history of cardiovascular disease, family history of cancer, quintiles of fruit and vegetable, red meat, starchy foods consumption, and total energy intake. In addition, a quartile analysis of the same study showed that higher intake of saturated fatty acids from dairy sources was not significantly associated with total mortality (HR= 0.87, p = 0.26), or major cardiovascular disease (HR= 0.94, p= 0.39).[282] Finally, in a meta-analysis of prospective cohort studies (follow up range 5-25 years) including 938,465 adults, whole fat vs. reduced fat dairy intake was not associated with mortality, cardiovascular disease or coronary heart disease.[283]

Saturated fat intake has been associated with higher LDL concentration,[284] which is predictive of cardiovascular disease risk. One prospective cohort study of 2890 Canadian children aged 2-8 years identified that children who consumed higher cow's milk fat had higher circulating non-HDL cholesterol concentrations (every 1% increase in cow's milk fat was associated with a 0.024 mmol/L (p= 0.01) increase in non-HDL cholesterol), but consuming higher cow's milk fat was not associated with high non-HDL cholesterol.[230] Two controlled trials identified that children who switched from consuming whole to reduced fat milk over 4-6 months resulted in lower circulating LDL cholesterol concentrations when compared between groups, but results for total and HDL cholesterol were inconsistent between the studies.[285,286]

Several studies have documented a relationship between higher cow's milk intake and lower serum cholesterol concentrations, despite the relatively high cholesterol and saturated fat content of cow's milk.[287] Saturated fat from cow's milk appears to have a different effect on serum cholesterol than other saturated fat-containing foods.[288] This different effect is hypothesized to occur because of fermentation of indigestible carbohydrates in the intestine, which may change cholesterol metabolism and result in lower circulating cholesterol in the blood.[289] Calcium may also bind some dietary cholesterol in the intestine and cause it to be excreted rather than absorbed.[290] A recent meta-analysis of RCTs evaluating the effect of presence of any dairy, as well as whole vs. reduced fat dairy intake on serum cholesterol revealed no evidence of a difference in serum LDL or HDL concentrations among adults.[291]

In terms of cardiometabolic risk factors, higher cow's milk intake has been associated with lower circulating triglycerides, IL-6, TNF-alpha, CRP and risk of hypercholesterolemia,[292] and higher HDL cholesterol among adults after adjustment for factors including age, sex, smoking, physical activity, BMI, blood pressure, total and HDL cholesterol values, triglyceride levels, education, alcohol consumption, birthplace, use of medication, and average weekly consumption of food groups.[293] Higher milk intake has not shown a relationship with higher risk of stroke, CHD or mortality in adulthood.[277] Lower risk of type 2 diabetes has also been documented in adults who consume more cow's milk than those who consume little or none.[294] A number of mechanisms have been postulated to account for these relationships, though no clear understanding of a single or synergistic mechanism is known to date. Further research is needed on several cardiovascular and metabolic outcomes assessed together in association with dietary factors such as cow's milk, since evaluation of one cardiometabolic marker gives only a limited understanding.[288]

Low vitamin D has consistently been associated with inflammation in the body.[295] Given that cow's milk is the main dietary source of vitamin D, cow's milk could offer cardiometabolic benefit through provision of vitamin D. This may be an important protective relationship due to the higher average consumption of cow's milk during childhood compared to adulthood in most populations,[62] and the emerging evidence that cardiometabolic risk factors begin to develop during childhood.[296]

Among children, a longitudinal study followed 335 children from 18 months to 8 years of age and revealed that those who consumed at least 2 servings of cow's milk per day had lower blood pressure later in childhood than others who consumed less, after adjustment for age, sex, physical activity, smoking, glycemic load, fibre and energy intake, family history of type 2 diabetes, serum cholesterol and triglycerides, blood pressure, and BMI.[297] Another prospective cohort study of children aged 3-6 years confirmed this finding after adjustment for parent education, parent and child age and BMI, height, physical activity, and dietary intake of energy from fat.[298] A large (N= 13,486) cross-sectional study of Iranian children aged 6-18 years showed no evidence of a difference in systolic or diastolic blood pressure between those who consumed whole vs. reduced fat cow's milk.[299] Two meta-analyses revealed similar associations between higher cow's milk intake and lower risk of hypertension among adults.[280,281] Meta-regression in one analysis showed evidence of a stronger relationship among adults with overweight.[280] The other meta-analysis included large studies which adjusted for BMI, which is an especially relevant confounder.[281]

Though it provides a long-term estimate of the association between cow's milk and cardiometabolic health, much of the available evidence on this topic is observational and would benefit from additional intervention studies to clarify cause-and-effect relationships.

2.2 Nutritional requirements and recommended intakes for children

2.2.1 Infancy (<1 year of age)

Breastfeeding infants are typically provided with approximately 5-10% protein, 50% fat, and 40-45% carbohydrate (as % energy) from human breast milk. The WHO has estimated the daily infant (age 0-6 months) energy requirement as 86 kcal/kg/day, protein requirement as 9.1 g, fat as 31 g and carbohydrate as 60 g.[300] Breastmilk provided to term infants has been shown to contain about 1.2 g protein, 3.6 g fat and 7.4 g lactose, which together provides 70 kcal per 100 mL,[301] though it is known that both composition of breast milk and infant nutrient requirements fluctuate depending on child age, maternal diet, and a number of other factors. Similar to cow's milk, breast milk fat is complex and comprised of over 200 different fatty acids, depending on maternal diet and stage of lactation.[302] Protein composition is also influenced by maternal factors and can include 400 unique proteins.[302] Casein only comprises 13% of the protein fraction of human breast milk, which is the lowest of all mammalian milks and has been suggested to correspond to the slow growth rate of human infants relative to other mammals.[303]

Guidelines from the CPS, Dietitians of Canada and Health Canada advise that parents wait until age 9 months to introduce fluid cow's milk to children.[304] The AAP suggests that children should drink breast milk or formula for the first year of life, but also that children may start to consume cow's milk at age 12 months.[305,306] The WHO suggests that breast milk is to be provided exclusively for the first 6 months of life, but is still important beyond 6 months of age once complementary foods are introduced, up to age 2 years.[307] Evidence for an "optimal" dietary transition from breast milk or infant formula to other solid foods is limited. The AAP and CPS recommend to exclusively breast- or formula-feed children until age 6 months,[50] but according to the AAP, "current [toddler] feeding practices and guidelines are influenced by small-scale studies of infant feeding behavior, idiosyncratic parental behavior, and popular opinion."[53] Randomized controlled trials to determine best practices for toddler feeding are needed.

2.2.2 Childhood (1-18 years of age)

The CPS and Canada's Food Guide recommends children (age 1-18 years) consume fresh fruits and vegetables, whole grains, dairy and meats through home cooked meals. Families are suggested to limit refined sugars and fruit juice, as well as foods high in saturated fat such as lard and butter, and processed meats such as lunch meats. Instead, children should be provided with water to drink and sources of omega-3 and omega-6 fatty acids.[49,51] The AAP recommends a diet primarily composed of fruits and vegetables, whole grains, low- and non-fat dairy products, beans, lean meats and fish for children over age 2 years.[53] Guidelines also emphasize that children's diets should be low in saturated and trans fats, sodium and sugar, and provide adequate micronutrients.[308]

Health Canada provides recommendations for macronutrient intakes in children (Table 4). Recommendations are given in both grams per day (RDA or AI) and percent of total daily energy in kilocalories (Acceptable Macronutrient Distribution Range; AMDR).

Table 4. Health Canada recommended Dietary Reference Intakes for children 1-18 years of age for macronutrients.[204]

<table>
<tr><th colspan="2" rowspan="2">Child age and sex</th><th colspan="2">Protein</th><th colspan="2">Carbohydrate</th><th colspan="2">Total fat</th><th colspan="2">Alpha-linolenic acid (n-3)</th><th colspan="2">Linoleic acid (n-6)</th></tr>
<tr><th>RDA (g/day)</th><th>AMDR (% energy)</th><th>RDA (g/day)</th><th>AMDR (% energy)</th><th></th><th>AMDR (% energy)</th><th>AI (g/day)</th><th>AMDR (% energy)</th><th>AI (g/day)</th><th>AMDR (% energy)</th></tr>
<tr><td colspan="2">1-3 years</td><td>13</td><td>5-20</td><td rowspan="6">130</td><td rowspan="6">45-65</td><td rowspan="6">ND</td><td>30-40</td><td>0.7</td><td rowspan="6">0.6-1.2</td><td>7</td><td rowspan="6">5-10</td></tr>
<tr><td colspan="2">4-8 years</td><td>19</td><td rowspan="5">10-30</td><td rowspan="5">25-35</td><td>0.9</td><td>10</td></tr>
<tr><td rowspan="2">9-13 years</td><td>Females</td><td>34</td><td>1.0</td><td>10</td></tr>
<tr><td>Males</td><td>34</td><td>1.2</td><td>12</td></tr>
<tr><td rowspan="2">14-18 years</td><td>Females</td><td>46</td><td>1.1</td><td>11</td></tr>
<tr><td>Males</td><td>52</td><td>1.6</td><td>16</td></tr>
</table>

RDA: Recommended Dietary Allowance; AMDR: Acceptable Macronutrient Distribution Range; AI: Adequate Intake; ND: Not Defined

2.2.3 Fat guidelines

In the 1970's, the American Heart Association recommended a low fat diet, focused on reducing saturated fat and cholesterol, for the prevention of coronary heart disease. This recommendation extended to children, and specified that only 30% of daily energy should come from dietary fat (10% of total daily energy from saturated fat), 15% from protein and 55% from carbohydrates.[309] Recent analyses have determined that at that time and presently, there is insufficient evidence from RCTs and prospective cohort studies to support this guideline.[310-312]

Over time, recommendations have become more liberal about the contribution fat should make to the diet. Though AMDRs still exist from Health Canada, the 2019 Canada's Food Guide does not provide quantity recommendations; instead, it suggests to "choose foods with healthy fats instead of saturated fat."[49] The 2015-2020 Dietary Guidelines for Americans[313] also avoided prescriptive recommendations by stating "a healthy eating pattern limits saturated and trans fats." Though these guidelines show progress reflecting recent evidence, both may benefit from conducting updated literature reviews on health outcomes associated with dairy fat, given that fat-free and low-fat milk are still emphasized.

When recommendations for limiting dietary fat were first introduced, the AAP questioned it based on evidence that fatty streaks could be found in the arteries of children regardless of dietary or lifestyle factors[314] and lack of established relationships between diet and cardiovascular risk factors in children.[315] At that time, the AAP made a recommendation for 30-40% of daily energy intake to come from fat for children younger than 18 years of age.[316] The evidence supporting this recommendation was substantiated on knowledge that fat encourages adequate growth and development, and trends suggesting higher fat intake was associated with taller height in children: as children were better nourished after World War II, worldwide trends showed children were growing taller. Though better growth was likely not attributed to only fat intake; rather a wide variety of dietary and non-dietary factors were likely involved, this recommendation for 30-40% of daily energy from fat for children exists at the present time.[317]

Canadian guidelines from the 1993 Joint Working Group of the Canadian Pediatric Society and Health Canada stated, "From the age of two until the end of linear growth, there should be a transition from the high-fat diet of infancy to a diet that includes not >30% of energy as fat, and not >10% of energy as saturated fat."[318]

Before the introduction of complementary solid foods (defined as anything besides water, breast milk or fortified infant formula), an infant fed according to recommendations has a diet in which fat comprises 50-55% of the diet. After introduction of solid foods, this proportion usually reaches 30% or less by 9-12 months of age.[319,320] Though it is known that dietary fats, especially n-3 PUFAs such as DHA, are required for infant growth and brain development, the effects of a high or low fat diet beyond introduction of complementary foods during early childhood have not been well studied. Until 2012, there had been no longitudinal studies which have demonstrated an adverse effect of a relatively high fat intake (40% energy) through 24 months of age.[320]

Very low fat diets (defined as ~20% of energy from dietary fat) in children are also not well evaluated in the literature. Children who consume <80% of their recommended total energy intake have been shown to experience linear growth stunting when dietary fat intake comprised <20% of daily energy intake.[321] Vegetarian children who tend to consume lower fat diets may experience slower growth, but the possible mechanism is unknown and data on this relationship needs updating.[317] A RCT of overweight and obese children aged 6-12 years who followed various weight loss regimes (quantity of dietary fat recommended or consumed not recorded) over 13 months showed that children following low fat diets did not reach their expected heights at 5 years post-enrolment.[322] Lower fat diets can also limit important nutrients found in fat-containing foods, such as fat soluble vitamins, zinc, iron and calcium, all of which are important for child growth and development.[321]

The AMDR from Health Canada for fat in children's diets is 30-40% of total daily energy intake for children aged 1-3 years, and 25-35% of daily energy intake for children aged 4-18 years. However, Canadian dietary guidelines for healthy term infants state, "there is no evidence that [fat] restrictions provide any benefits during childhood."[50] For all age groups, saturated fat is recommended to comprise less than 10% of daily energy intake. The adequate intake (AI) levels for linoleic acid (n-6 polyunsaturated fat) are 7 g/day for children aged 1-3 years, 10 g/day for 4-8 year olds, 12 g/day for 9-13 year olds, and 16 g/day for 14-18 year olds. For alpha-linolenic acid (n-3 polyunsaturated fat), the AI is 0.7 g/day for children aged 1-3 years, 0.9 g/day for 4-8 years, 1.2 g/day for 9-13 years, and 1.6 g/day for 14-18 year olds.[204]

2.3 Childhood adiposity

The human body is composed of organ, nervous, muscular, connective, and adipose tissues, which include subcutaneous and visceral fat. Multiple techniques have been used to measure the proportion of adipose tissue in the body including DXA (Dual X-ray Absorptiometry) which involves x-rays to quantify body fat,[323] air displacement technology to measure adipose tissue, magnetic resonance imaging, skinfold measurements and the Body Mass Index (BMI).[324] Though highly accurate and sophisticated, both DXA and air displacement technology are costly, time consuming, and impractical to perform in routine clinical settings. Skin fold measurements and BMI are more practical, though these less precise measures which can be used in short clinical encounters.[325] Skinfold measurements use calipers to grip specific areas of skin where adipose tissue tends to accumulate: the triceps and bicep area of the arm, and subscapular region. The width of the skinfold thickness corresponds to the amount of fat tissue estimated under the skin.[326] Bioelectrical impedance is used to assess tissue water quantities given known water-retaining properties of fat and muscle tissues using bioelectrical frequencies.[327] BMI is currently the standard adiposity measurement used in clinical care for both adults and children. BMI compares a person's height to weight and categorizes individuals into underweight, normal weight, overweight, and obese weight classes. BMI is calculated using the formula: weight (kg) divided by height squared (m^2).[328] In children aged 2 to 19 years, BMI-for-age, or a BMI z-score (zBMI), is used to adjust a child's weight-for-height ratio to their age. BMI z-scores correspond to standard deviation scores away from the 50th percentile in growth curves for child weight for age, length for age, and weight-for-length for age or BMI for age (depending on the child's age). For children younger than 2 years, weight-for-length is used and interpreted in the same way as zBMI.[329] Evidence suggests that weight-for-length and zBMI are similar and may be used interchangeably.[330] According to Flegal & Ogden, "a BMI z-score or percentile represents a measure of weight, adjusted for height, sex, and age, relative to a smoothed reference distribution, and not simply a measure of weight and height for a child."[328] zBMI is a commonly used clinical indicator used for weight status screening in children,[331] due to its relative ease of measurement and interpretability, non-invasiveness and ability to follow over time.[332] Though DXA and air displacement measures are superior in quantifying body fat, zBMI correlates with body fat and is a known predictor of future obesity and health issues.[333] Clinicians and families find BMI and zBMI to be interpretable reference points for tracking body weight over time.[334] However, BMI and zBMI categorize a continuously measured attribute, which may categorize people arbitrarily (for example, zBMI values of 1.9 vs 2.1 are categorized differently). Categorizing individuals with very high BMI values (> 97th percentile) is based on limited data, thus should be interpreted with caution.[335] This method also does not quantify body fat, distinguish lean from fat mass, or assess the proportion of body fat in different regions of the body.[336]

zBMI can be categorized three ways, using: the World Health Organization standards (WHO) developed in 2008, the Center for Disease Control references (CDC) from the year 2000,[337] and the International Obesity Task Force cut-points (IOTF), also created in 2000.[338]

Compared to CDC and IOTF cut-points, WHO growth standards classify more children as overweight or obese based on BMI scores.[339,340] For this reason, the WHO standards are suggested to be the ideal growth curves to use when classifying children's weights.[332,340,341] The WHO standards are considered to reflect optimal child growth and the preferred set to use among the three. WHO growth standards provide a set of zBMI curves for children aged 2-19 years, which were derived from a multi-ethnic sample of children gathered by the WHO in between 1997 and 2003 (*see Appendix: 8.1 WHO BMI-For-Age Curves & Canadian BMI Growth Curves*). These children were from Brazil, Ghana, India, Norway, the USA, and Oman, and were predominantly breastfed and raised in a healthy environment based on criteria such as non-smoking households in non-economically deprived environments that were likely to interfere with their growth and receiving routine health care.[342] It is well established that social determinants of health, defined by the WHO as "the conditions in which people are born, grow, work, live, and age, and the wider set of forces and systems shaping the conditions of daily life,"[343] influence the way children grow and develop. For this reason, the WHO growth standards sampled from communities without economic disadvantages to reduce the likelihood of compromised growth due to sub-optimal living conditions.[344] Weight status of children aged 0-2 years are measured using weight-for-length z-scores, which have been shown to be interpretable interchangeably with zBMI.[330] Curves are segmented into percentiles and z-scores that represent standard deviations from the mean (50^{th} percentile). When interpreting a growth curve, z-scores can be used to numerically determine a child's growth in reference to the sample cohort of children used to develop the reference or standard.[328,331] Table 5 provides the WHO recommended standardized terminology used to describe a child's zBMI or weight-for-length score derived from WHO growth curves.[331,345]

Table 5. WHO recommended zBMI descriptive terminology for children aged 2-19 years.

Z-SCORE	Interpretation for children aged 5-19 years	Interpretation for children aged 2-5 years
<-3	Severe thinness	Severe thinness
-2 to -3	Thinness	Thinness
-2 to 1	Normal	Normal
1 to 2	Overweight	Risk for overweight
>2	Obesity	Overweight
>3	Severe Obesity	Obesity

2.3.1 Childhood overweight and obesity in Canada

Over the past 30 years, the proportion of Canadian children classified as having overweight or obesity has risen and the proportion of children considered to have healthy weight has decreased.[346] In Canada, about 1 in 3 children and adolescents has overweight or obesity.[347] Data from the 2004-2013 Canadian Health Measures Survey (CHMS) indicated that the number of children living with overweight or obesity has decreased though, from 30.7% to 27.0%. Measurements for these data were taken by trained staff to the nearest 0.1 kg for weight and 0.5 cm for height. [348] Since 2007, obesity rates in Canadian children have stabilized at about 13%. Boys, adolescents, and non-white children were more likely to have higher zBMI scores in this survey.[349] Children in Indigenous communities were at a heightened risk of having overweight or obesity, with 30% of Canadian Indigenous youth <18 years old living with overweight and 26.5% living with obesity.[350]

2.3.2 Dietary fat and child adiposity

Dietary fat has traditionally been believed to stimulate energy storage in the form of adipose tissue.[351] The energy contribution per gram of fat (9 kcal/gram) is higher than that of protein and carbohydrates (each 4 kcal/gram), and there is higher efficiency in storing fat rather than carbohydrates after ingestion because of a lower thermic effect for fat,[352] which refers to the energy required to metabolize and store ingested nutrients.[353] However, studies which consider ratios of dietary carbohydrate, protein and fat and weight status have yielded conflicting results, suggesting that dietary fat does not independently influence adiposity.[354,355] One consistent finding has been that total energy intake regardless of source was the main predictor of weight status.[356] Another factor is dietary behaviour; passive eating, or consumption regardless of hunger, combined with high fat foods also can contribute to excess adiposity. When foods higher in fat are passively consumed, they present the highest risk of excess energy intake, which is known to contribute to weight gain.[356] Other important factors that may influence the relationship between dietary fat intake and adiposity include the type of fat consumed (saturated, trans, or unsaturated), the food source (made using nutritionally refined ingredients or natural; fresh or shelf-stable), other nutrients found in fat-containing foods such as fibre or calcium, endocrine response, genetics, and physical activity.[357-359] Social determinants of health such as income, access to a variety of nutrient-dense foods and knowledge of how to prepare them, access to physical activity and recreational resources, and living conditions also likely play an important role in this relationship.[360] However, given the number of hypothesized mechanisms and possibility that many of them overlap, individual or synergistic effects are challenging to diferentiate.[227] Further, these factors interact differently across the life course, particularly in children where periods of growth alter metabolic processes.[361,362]

Numerous observational studies[14,357,363-368] have found that children with higher dietary fat intake do not have higher adiposity. A prospective cohort study which involved 140 children from Australia followed from age 3 months to 8 years found that dietary fat intake was not associated with higher adiposity at ages 2, 4 and 8 years.[369] However, more long-term, large cohort studies and randomized controlled trials are needed to fully explore this relationship. On the other hand, lower dietary fat intake has been associated with higher sugar consumption throughout childhood.[369] Over the past 30 years, there has been a steady decline in childhood dietary fat intake, a concurrent rise in sugar consumption.[1,370]

A Cochrane review which evaluated dietary fat intake with anthropometric and serum lipid outcomes included 3 RCTs and 21 prospective cohort studies of children aged 2-18 years without intention of weight loss. The types of interventions (in the RCTs only) included different dietary counselling techniques for parents or children in different settings and outcome measures were varied, including body fat percentage, zBMI, and serum triglycerides and cholesterol concentrations. The overall study quality was considered low according to GRADE criteria. Despite these limitations, baseline lower fat intakes were associated with lower total and LDL cholesterol, but no evidence was found for differences in body weight or in other biochemical markers.[371]

2.3.3 Evidence for dietary obesity prevention strategies in children

The literature on dietary obesity prevention strategies in children is challenging to interpret because of differences in participant populations, intervention intensity and duration, design and delivery methods, which vary widely between studies. A 2019 Cochrane Review identified 153 studies about obesity prevention interventions in children. Among children aged <5 years, there was moderate certainty evidence that interventions for diet and physical activity combined were effective in slightly lowering zBMI (among 16 RCTs, MD -0.07, 95% CI -0.14 to -0.01). Dietary or physical activity interventions alone were not effective in this age group. For children aged 6-12 years, there was low-certainty evidence to suggest interventions targeting both diet and physical activity were effective in lowering zBMI (among 20 RCTs, MD –0.05, 95% CI –0.10 to –0.01), but again, dietary or physical activity interventions alone did not show evidence of effects on zBMI.[372] In both age groups, no differences were observed between intervention settings (home, child care or school). Authors of this review suggested that variability between intensity and duration of interventions, targeted foods, beverages, habits or activities, settings, and individuals involved (entire families vs. individual children) contributed to the low magnitude of overall observed effect. Characteristics of successful interventions in early childhood included strategies to increase breastfeeding instead of formula feeding, which may protect against excess childhood adiposity.[373] Other successful interventions encouraged families to pack healthy lunches including fruits, vegetables, and water, and provided parents with tips for "picky eaters."[374,375] Behavioural strategies including caregiver role modeling, family meals, encouraging dietary diversity and promoting parental awareness and responsiveness to hunger cues may contribute to healthy eating habits and lower risk of overweight or obesity.[376] Strategies which have also shown promise include those that help families make nutrient-rich dietary choices, embracing a holistic approach to healthy eating, physical activity, sleep, mental health and supportive school and community environments.[377-379] However, they are expensive, time consuming and challenging to involve families that are most at risk. Dietary strategies can become diluted by different families taking varied approaches in the same over-arching "healthy eating" interventions, which makes identifying foods or behaviours that contribute to obesity prevention challenging. The generalizability and applicability of RCT interventions for obesity has also been questioned. One study evaluated how 10 obesity prevention and treatment interventions in study settings compared to scaled-up versions implemented in communities, and found that effects observed in RCTs were 75% or less once scaled up.[380]

2.4 Evidence on the relationship between cow's milk and adiposity

Cow's milk may exert effects which limit excess adiposity due to a number of synergistic factors, including satiety, endocrine response, whey and casein protein effects, glycemic control, calcium and vitamin D, and dairy fat.[381] A systematic review and meta-analysis of 17 randomized controlled trials which sought to examine the relationship between cow's milk intake and various anthropometric outcomes in children and adolescents did not find differences in height, waist circumference, or fat mass among children aged 6-18 years who received cow's milk interventions than controls. However, cow's milk consumers had higher body weight gain (0.48 kg, 95% CI 0.19 to 0.76 kg), lean mass (0.21 kg, 95% CI 0.01 to 0.41 kg), and attenuated gain in percentage body fat (-0.27%, 95% CI -0.45% to -0.09%) than controls, suggesting that cow's milk may moderate body composition, favouring lean mass.[382] Similarly, a systematic review of dairy product intake which examined 35 intervention and observational articles on dairy intake, body composition and energy balance in children aged 2-18 years found a relationship between higher dairy intake and lower body fat, BMI and energy balance (defined as the relationship between dietary energy vs. energy expenditure) from the observational studies.[223] Five randomized controlled trials were included in this analysis but found no evidence of an overall relationship, although one study showed an inverse relationship; that is, dairy rich diets led to lower BMI gain and attenuated rises in circulating triglyceride, insulin and homeostatic model assessment of insulin resistance (HOMA-IR) concentrations among overweight children compared to diets which did not emphasize dairy.[223,383] Though this systematic review included studies dairy foods other than cow's milk (yogurt, cheese, butter, etc.), mechanisms may be shared between dairy foods.

Few studies have examined the relationship between cow's milk intake and weight loss in children. One randomized controlled trial of overweight children aged 8-10 years assigned participants to either an average of 1.3 or 4 servings of cow's milk daily for 16 weeks. The objective of the trial was to determine if there were any anthropometric or metabolic effects of high vs. low cow's milk consumption. There was no evidence of a difference between groups at study conclusion; however, part of the provided milk to both groups was sweetened milk and children in the "low milk" group were also consuming 3 servings of other sugar sweetened beverages per day, likely leading to an overall higher energy intake in both groups.[384] Similarly, among 91 adolescents aged 10-15 years who consumed dairy products while undergoing an obesity treatment RCT over 12 months showed higher adiposity losses compared to children who did not consume dairy (-0.005 in zBMI per daily serving of dairy, 95% CI -0.01 to -0.001), but after adjustment for physical activity and other dietary factors, evidence for this relationship was weakened.[385]

Several more recent observational studies have had conflicting findings on the relationship between cow's milk consumption and excess childhood adiposity. A cross-sectional which study included 903 Azorean children aged 15-16 years showed that consumption of at least 2 servings of dairy foods per day was associated with lower odds of abdominal obesity (boys: OR= 0.22, 95% CI 0.08 to 0.63; girls: OR= 0.56, 95% CI 0.31 to 1.02) after adjustment for age, BMI, pubertal stage, physical activity level, energy intake, calcium-to-protein ratio and dietary fibre.[386] Several cross sectional studies have identified that children who consumed above average quantities of dairy per day (≥3 servings/day) had lower BMI scores than those who consumed below average quantities.[387-389] Conversely, some longitudinal studies have suggested that a higher volume of milk consumed increases energy in the diet resulting in higher BMI.[39,390] One prospective cohort study included a nationally representative sample of 12,829 American children in the Growing Up Today Study (a branch of the Nurses' Health Study) over a 5 year period. The study revealed that children who consumed 3 servings of dairy per day had higher BMI gains (boys: +0.07, 95% CI 0.03 to 0.11, p= 0.04; girls: +0.09, 95% CI 0.06 to 0.12, p= 0.007) than those who consumed 1-2 servings per day, which appeared to be predicted by higher energy intake.[39] Most, but not all of these observational studies controlled for relevant potential confounders such as age, sex, calcium intake, physical activity, total energy intake, food insecurity, parent anthropometry and puberty stage. Ideally, future studies would consistently account for as many potential confounders as possible.

Methodological issues may contribute to inconsistent evidence about the relationship between cow's milk intake and child adiposity. The majority of studies have been observational which are able to describe associations but are not able to establish cause and effect relationships. While prospective cohort studies offer a better estimate of temporality of the observed relationships than cross-sectional studies, in the absence of randomization it is difficult to separate pre-existing potentially confounding factors related to dietary intake, social determinants of health and adiposity such as reasons for choice of food provided to children, which may lead to observed reverse causality. Additional potential sources of bias regardless of study design include measurement bias for dietary measures because of reliance on memory, under-reporting, and social desirability bias.[72] Obtaining dietary data from children can be challenging with foods provided in different settings (home, school, daycare, etc.) and often relying on parental recall. Though recognized by the WHO as an acceptable measure of adiposity, convenient proxy measures of body weight such as zBMI do not distinguish lean from fat mass, while more rigorous measurement methods such as DXA are time consuming, expensive, and impractical to administer in clinical settings and are therefore less desirable for clinical researchers and participants. As a result, outcome measures such as zBMI may misclassify weight status among children, leading to biased results.

A narrative review and meta-analysis of observational and intervention studies on the relationship between cow's milk consumption and adiposity in adults reported that cross sectional and prospective cohort studies had poor quality and conflicting results.[381] However, the largest observational study included in this review was a Portuguese cross sectional study of 37,513 adults which demonstrated an association between higher cow's milk intake and lower BMI (men: -0.11, $p< 0.001$; women: -0.06; $p< 0.001$ per daily serving of milk) after adjustment for age, region, physical activity, smoking, dietary intake and educational level.[391] A systematic review and meta-analysis was conducted on RCTs of dietary interventions including cow's milk on measures of body weight and composition. The study included 37 RCTs of 184,802 adults for periods of 1-36 months and revealed that dairy interventions led to increased lean body mass (0.37 kg, 95% CI 0.11 to 0.62) and decreased WC (-1.37 cm, 95% CI -2.28 to -0.46), but there was no observed total body weight change (0.01 kg, 95% CI -0.25 to 0.26). When interventions were energy restricted (intended for weight loss), there was evidence that the cow's milk interventions resulted in lower body weight (−0.64 kg, 95% CI −1.05 to −0.24), body fat (−0.56 kg, 95% CI −0.95 to −0.17), and WC (−2.18 cm, 95% CI −4.30 to −0.06).[392]

2.4.1 Possible mechanisms for the relationship between cow's milk and adiposity

Calcium contained in cow's milk may play a role in adipose metabolism[393-395] as it is known to regulate intracellular lipid metabolism and triglyceride storage.[396] A meta-analysis which evaluated the relationship between dietary calcium and BMI among adults revealed that an additional 800 mg of dietary calcium per day was associated with a 1.1-unit lower BMI.[381] Another meta-analysis of 33 RCTs and longitudinal studies determined that children and adolescents (N= 4733) were more likely to experience a negative correlation between calcium intake and weight change than adults.[397] Adipose tissue has been shown to be responsive to parathyroid hormone and 1,25-hydroxyvitamin D_3, which regulate circulating and intracellular calcium concentrations.[37] Increased dietary calcium is believed to inhibit lipogenesis and promote lipolysis by suppressing 1,25-dihydroxyvitamin D_3, which tends to promote intracellular lipogenesis and suppress lipolysis in adipocytes.[37] In other words, lower dietary calcium intake favours energy storage (lipogenesis) and higher calcium intake favors energy utilization (thermogenesis).[398] Dairy foods may further amplify the possible benefit of calcium on adiposity. Two randomized controlled trials of obese adults showed that greater weight loss was achieved among individuals who consumed an energy restricted (500 kcal/d deficit according to individual needs), high-dairy diet compared to isocaloric diets with high- or low-supplemental calcium over a 6 month period.[399] Investigators suggested this may have been due to synergistic effects vitamin D contained in cow's milk facilitating calcium absorption with angiotensin-inhibiting effects of dairy proteins, which may have restrictive effects on lipogenesis.[399,400]

Vitamin D could contribute to the observed relationship between higher cow's milk intake and lower adiposity.[4] Vitamin D has an inverse relationship with adiposity, such that higher circulating serum 25-hydroxyvitamin D concentrations have been associated with lower measures of adiposity.[31,34,36,401,402] A study of over 42,000 adults which investigated the directionality between vitamin D levels and adiposity suggested that excess adiposity might be the initial trigger for lower circulating vitamin D concentrations, although numerous other factors such as diet and time spent outdoors may perpetuate both lower serum 25(OH)D concentrations and higher adiposity resulting in confounding.[403] It has been hypothesized that individuals with excess adipose tissue have less bioavailable vitamin D in circulation due to its fat soluble properties that sequester it into adipose tissues.[404] Higher body fat may reduce vitamin D's accessibility in serum for cells, bones and other tissues.[404,405] In addition, serum 25-hydroxyvitamin D has been shown to be associated with markers of inflammation in the body, such that higher levels of C-reactive protein are associated with lower 25(OH)D.[406] This observation suggests that inflammatory conditions, such as higher adiposity, may influence measures of circulating vitamin D. Another theory is that lower concentrations of vitamin D in the blood stimulate a rise in parathyroid hormone (PTH), which causes an influx of calcium into adipocytes, where lipogenesis then occurs.[37,396,407] To date, no study has identified the exact mechanism behind this relationship.

Compared to other beverages, cow's milk is nutrient-dense and has been shown to promote higher satiety. In children[408] and adults,[409] reduced fat (1% for children, 0.1% for adults) cow's milk and apple juice intake with breakfast were compared on satiety and subsequent energy intake in randomized crossover trials. Milk consumption resulted in lower energy intake at lunchtime and higher feelings of satiety 4 hours after breakfast in both groups.[409] However, total daily energy intake among children was not different between milk and juice drinkers.[408] These studies were conducted in controlled environments and relied on relatively low sample sizes, and additional evidence to support their findings is needed. Other similar studies have been conducted[410,411] but have shown inconsistent results. A meta-analysis was conducted on RCTs of dairy intake and energy consumption in subsequent meals and satiety. Among 13 included studies, results showed that dairy consumption led to higher satiety and lower energy intake at the next meal when compared to nothing, chocolate bars, or equal quantities of water, SSBs, or artificially sweetened beverages.[412]

Casein and whey proteins may play protective roles against excess adiposity, due to satiety-inducing effects.[413] Whey protein may also elicit a hormonal reaction where satiety hormones such as cholecystokinin and glucagon-like peptide 1 are released in response to consumption in a dose-dependent manner[414] and when compared to SSBs,[409] reducing hunger and possibly limiting future food intake.[105] Branched chain amino acids such as leucine which are prevalent in cow's milk may contribute to better glycemic control than other amino acids, contributing to prevention or treatment of obesity and other chronic disease.[415] In addition, the relatively low glycemic index score of lactose may aid in a slower release of glucose to the bloodstream, possibly leading to longer satiety and reduced hunger.[416] Cow's milk consumption has also shown to have a higher thermic effect than other beverages, indicating more energy is required to metabolize and store its nutrients, which may produce protective metabolic effects against excess adiposity.[417]

Dietary quality could contribute to the relationship between cow's milk and adiposity due to the contribution cow's milk makes to intake of various vitamins and minerals, but also dietary patterns typically associated with cow's milk consumption. Children aged 9-14 years in an NHANES analysis who consumed cow's milk had the highest Healthy Eating Index (HEI) scores, which is a validated measure of dietary quality.[66] Another study of children aged 1-5 years determined that dietary quality appears to be associated with beverage choice, such that higher dietary quality was predicted by higher intakes of dairy foods.[418] These findings were confirmed in a cohort of Australian children, where children who consumed cow's milk were more likely to meet daily micronutrient requirements than children who did not consume cow's milk.[69] However, these relationships are likely observed in part due to the varied and relatively high content of vitamins and minerals in cow's milk, which inherently would increase diet quality, regardless of other foods consumed. One study identified that children who consume higher cow's milk fat may have higher dietary quality, but these findings have not been repeated.[6] This study evaluated NHANES 2001-2002 data from children aged 2-5 years (N= 541) and observed that children who consumed whole milk most often had among the highest micronutrient intakes, but lowest Healthy Eating Index (HEI) score, and highest BMI scores. In contrast, children aged 6-11 years (N= 793) who typically consumed whole milk had the lowest BMI and among the highest HEI scores. Children from both age groups who consumed the most whole milk tended to consume the lowest amount of saturated fat.[6]

Evidently, there are numerous possible explanations for the mechanisms involved in the relationship between cow's milk and adiposity. Many studies do not account for the fat content of cow's milk, whether interventions encourage general cow's milk consumption regardless of fat or assume that reduced fat varieties must increase the likelihood of lower weight outcomes, or observational studies do not collect or analyze cow's milk fat intake. Though cow's milk fat may not be an intuitive factor in explaining weight loss or lower observed adiposity, some research suggests it may be an important detail to capture.

2.5 Cow's milk fat and adiposity

2.5.1 In children

For a summary of the literature on cow's milk fat and child adiposity, please refer to Chapter 3: *Cow's milk fat and childhood overweight: a systematic review and meta-analysis*. Since the publication of this article, some additional evidence has been made available. An analysis of NHANES data from children aged 2 to 20 years in 1999 to 2016 showed that children

(N= 26,750) who were living with overweight or obesity were less likely to consume whole cow's milk than those with normal weight. The analysis also revealed that children with overweight or obesity were less likely (OR= 0.77; 95% CI 0.60 to 0.98; p= 0.031) to consume whole milk directly after breast milk or fortified infant formula than those who had normal weight after adjusting for race, age, income, milk consumption frequency, and NHANES cycle.[419] An important detail in this nationally representative analysis is that families with children over age 2 years receiving WIC support are only provided with 1% fat cow's milk; 2% and whole milk are not covered. Though the NHANES analysis did not report the proportion of participants who received WIC support, in 2016, the eligibility rate of the total population of American women, infants and children was 51.5%, and of these 13.9 million families, 55% received WIC support.[420] The analysis did identify that children who were from households below the federal poverty level were less likely to consume whole milk directly after breast milk or infant formula than children from wealthier households.[419] Though this study may suggest reverse causality is involved in the observed relationship, many families receiving WIC support may not have had an option to select whole milk; thus, their findings that suggest whole milk are protective may be questioned due to the confounding effects of poverty which influences both food choices and risk of overweight.

Another systematic review and meta-analysis on dairy fat and child adiposity and cardiometabolic health[421] was also published following my review. The review identified 29 journal articles including 2 RCTs and 27 observational studies. Authors concluded that whole fat dairy was not associated with higher measures of adiposity in children and most evidence showed a relationship between higher dairy fat and lower child adiposity. Many identified studies in this review were also included in my systematic review and meta-analysis. Differences arose where studies included sources of dairy fat (i.e., cheese, yogurt) other than fluid cow's milk as exposures, or measures of cardiometabolic health rather than adiposity as outcomes. Authors did not conduct meta-analysis or assess studies for risk of bias.

2.5.2 In adults

Some adult observational research supports an association between higher cow's milk fat intake and lower adiposity and cardiovascular disease risk. A systematic review of observational studies found that whole milk was associated with lower adiposity in 11 of 16 studies of adults aged 18 years and older.[193] The largest study followed 19,352 Swedish women for 9 years.[422] Consumption of ≥1 serving of whole milk daily was associated with lower odds of ≥1 kg weight gain per year on average (OR= 0.85, 95% CI 0.73 to 0.99, p value not reported) whereas reduced fat milk was not (OR= 1.03, 95% CI 0.90 to 1.18).[422] This systematic review attempted to address the issue of reverse causality (i.e., lean individuals may choose higher fat dairy, and heavier individuals may choose lower fat dairy) through a subgroup analysis of the prospective cohort studies. When only prospective cohort studies were evaluated, four of six studies demonstrated a relationship between higher cow's milk fat and lower adiposity.[193] Some evidence does not support a relationship between higher cow's milk fat and lower adiposity. One recent prospective cohort study of 15,612 European adults over an average of 3.7 years showed that adults who increased their whole milk intake had increased BMI at follow-up (effect size not reported; $p < 0.05$) after adjustment for clinically relevant covariates. However, it was unclear how participants who may have consumed the same amount of whole milk over the study duration fared.[423]

A systematic review and meta-analysis of randomized controlled trials which examined adult consumption of whole vs. reduced fat dairy products and metabolic health revealed that weight gain was slightly higher among those who consumed reduced fat (0.82 kg, 95% CI 0.35 to 1.28 kg, p< 0.001) compared to whole fat dairy (0.41 kg, 95% CI 0.04 to 0.79 kg, p= 0.03) over a median of 26 weeks follow up, but no evidence of a difference in waist circumference; HOMA–IR; fasting glucose; LDL or HDL cholesterol, blood pressure or CRP was found.[291] An American prospective cohort study of 16,471 adult men reported that the highest quintile of baseline whole fat dairy intake was associated with 0.38 kg lower weight gain over the course of 12 years, in comparison to the lowest intake quintile of baseline whole fat dairy foods (p for trend= 0.03). In this study, there was insufficient evidence to suggest individuals who consumed the highest vs. lowest quantities of reduced fat dairy experienced weight change over the course of the study (+0.35 kg, p for trend=0.17).[424] A prospective cohort study of sixty-two 70-year old Swedish men which used validated dietary measures and serum pentadecanoic acid (C15:0) to measure cow's milk fat intake, limiting the potential for reporting or measurement error, found that higher dairy fat intake and higher serum C15:0 were associated with lower body weight, BMI, waist circumference, LDL:HDL ratio, and fasting plasma glucose.[425] Though the observed weight changes were small, cow's milk has been noted to increase lean body mass and lower fat mass, which may attenuate weight loss.[392]

A few adult observational studies have supported an association between higher milk fat intake and lower risk cardiovascular disease risk factors. In a prospective study of 2586 Scottish men, mortality from cardiovascular disease was lower among those who consumed whole cow's milk.[426] In a study of 2064 Dutch seniors, whole milk consumption was associated with lower systolic and diastolic blood pressure.[427] Further, among 3157 American adults, whole milk intake was associated with lower insulin resistance and better glucose homeostasis.[428] Ruminant-produced trans fatty acids have been suggested as a potential mechanism for these observations.[429] However, when examined together in systematic reviews and meta-analyses, the collective literature does not support a consistent relationship between higher dairy fat and better cardiometabolic health to date.[193,291]

Kratz et al.[193] suggested a hypothesis for varying observations about cow's milk and adiposity in adults: geography. Eight of nine European studies in their systematic review found a relationship between higher fat dairy and lower adiposity while the same relationship was seen in only three of seven North American studies. In Europe, dairy fat is considered healthier than in North America. Low total and saturated fat diets have been promoted and adopted to a greater extent in North America than in Europe.[430] Healthier lifestyles have been associated with higher dairy fat consumption in Europe, whereas smoking and low physical activity,[431] as well as lower SES have been associated with higher dairy fat intake in North America.[432] In North America, high fat dairy is often consumed in sweetened, carbohydrate-dense foods (i.e., ice cream, pizza), whereas in Europe it is more likely to be consumed as unsweetened yogurt, butter, or cheese, which are more likely to be fermented and may provide additional metabolic benefits.[193] Dairy farming in the United States and Canada can be highly industrialized, with large dairy farms producing high quantities of cow's milk. In Europe, dairy farms tend to be smaller and choose practices such as organic or grass fed dairy farming more often.[433] Many North American farms feed their cattle corn and soy, whereas European farms are more likely to pasture-feed their cows.[193] Pasture-fed cows produce milk with higher vaccenic acid, alpha-linolenic acid,[434] conjugated linoleic acid, and trans-palmitoleic acid, which have all been suggested as beneficial for lowering adiposity and improving metabolic health in humans.[193] American dairy farmers are permitted to use growth hormones and have lower production and quality standards than Europe and Canada, which have higher, stricter standards and do not allow hormone use.[435,436]

2.5.3 **Hypothesized biological mechanisms**

2.5.3.1 Satiety

Whole milk is believed to delay gastric emptying compared to reduced fat milk.[437] This may induce satiety, limiting additional energy intake, which could lower overall energy intake and reduce excess adiposity. Whole milk may induce satiety through the release of hormones such as cholecystokinin (CCK), which reduces desire for other foods.[21] CCK is a hormone released in response to consumption of fat and protein, and acts as a hunger suppressant.[438] CCK has been shown to slow gastric emptying, inhibit food intake and may play a role in controlling the glycemic response to a meal.[439] Following cow's milk intake, plasma CCK concentrations remain elevated for approximately 90 minutes,[107] during which energy intake may be suppressed. Dairy fat may elicit higher CCK responses and lower insulin responses than other sources of dietary fat.[440] Glucagon-like peptide-1 (GLP-1) release may also play a role in satiety and slowed gastric emptying.[441] Both carbohydrate and fat cause secretion of GLP-1, in addition to cow's milk proteins regardless of presence of fat or carbohydrates.[442,443] Leptin, another hunger suppressing hormone, is triggered by fat and energy intake and opposed by ghrelin, a hunger stimulant.[444] In non-obese individuals, leptin may signal the release of GLP-1, which may contribute to its satiety-inducing characteristics.[445] These hormonal responses, combined with satiety exerted by whey and casein proteins, make cow's milk a metabolically unique food.

Another factor which may contribute to satiety following cow's milk ingestion is the relatively low glycemic response it elicits relative to foods containing similar amounts of other carbohydrates. Foods with higher glycemic index values cause a higher insulin response and offer limited satiety.[14] Higher GI foods may direct nutrients from oxidation to storage, possibly adding to adipose tissue.[446] A RCT of adolescent boys which compared cow's milk to fruit juice consumption for 28 days found that regular cow's milk consumption appeared to elicit a higher glucagon response when compared to fruit juice, and led to a lower rise in blood glucose concentration following consumption. Also, compared to fruit juice, regular cow's milk consumption resulted in lower total energy intake (-155 kcal per day, 95% CI -309 to -2 kcal, p= 0.048).[447] A randomized crossover trial of children aged 10-12 years with obesity compared breakfast consumption with whole cow's milk, reduced fat cow's milk and apple juice on satiety and energy intake at lunch. Whole cow's milk consumption resulted in higher satiety than reduced fat cow's milk 4 hours after breakfast, but did not lower total energy intake.[448] Together, these findings suggest that cow's milk consumption may moderate satiety and subsequent energy intake, but further research is needed.[447]

2.5.3.2 Growth rate

Whole and reduced fat cow's milk contain the same quantity of protein by volume, but whole milk provides a lower proportion of protein and a higher proportion of fat, which is suggested to be metabolically protective to young children who have rapid growth.[13,449] A lower fat, high protein diet (defined as >15% protein[450]) in early childhood may promote faster growth during childhood, which is suggested to related to earlier adiposity rebound (the point that BMI reaches a nadir after infancy[451]),[452] which also has been associated with a higher risk of obesity in adulthood.[451,453,454] In one prospective cohort study, infants 0-24 months of age who had larger gains in length and weight also had a higher risk of obesity at age 14 years. Higher length gain was associated with more body fat stored around the abdomen, but weight gains were not.[455] This body fat pattern in children has been associated with higher risk of cardiovascular disease later in life.[456] Another prospective cohort study revealed that children with lower dietary fat intakes at age 2 years of age had higher fat mass and circulating leptin concentrations at 20 years of age.

For each 1% increase in energy consumed from fat at age 2 years, adults had 0.31 kg lower fat mass at age 20 years (95% CI –0.60 to –0.01 kg, p= 0.04). Investigators of this study suggested that these findings may have resulted from adaptive energy storage mechanisms in early life, which was carried over the life course.[457] Additional studies are required to support and add detail to this theory.

2.5.3.3 Sugar Sweetened Beverages

Sugar sweetened beverages (SSBs) have been defined as "any liquids that are sweetened with various forms of added sugars like brown sugar, corn sweetener, corn syrup, dextrose, fructose, glucose, high-fructose corn syrup, honey, lactose, malt syrup, maltose, molasses, raw sugar, and sucrose."[313] Consumption of SSBs has been associated with sedentary behaviour, smoking, and higher screen time,[458,459] but also independently associated with higher adiposity in children.[460,461] SSBs typically have no nutritional value other than approximately 100 kcal per 250 mL provided by sugars. For this reason, they do not offer the satiety associated with consuming solid foods or beverages containing protein or fat.[462] Over the past 30 years, consumption of cow's milk has declined among children in North America,[463,464] and appears at least in part to be compensated by higher consumption of SSBs. In the USA in 2010, SSBs were estimated to account for an average of 8% of total daily energy intake among children.[465] Children who consume SSBs instead of cow's milk are trading off a more nutrient-dense food with a less nutrient-dense one, which does not offer the satiety provided by cow's milk. Children who consume SSBs have been shown to have poorer quality diets[466] suggesting that additional energy intake following SSB consumption may include other nutrient-poor foods.[467,468] Added sugars from SSBs has been associated with higher overall energy intake and higher body weight. Among 613 Canadian children aged 8-10 years in the QUebec Adipose and Lifestyle

InvesTigation in Youth (QUALITY) study, each 10 g higher consumption of added sugars from SSBs was associated with 0.4 lower daily servings of fruit and vegetables, 0.4 higher BMI, 0.5 kg higher fat mass and 0.9 cm higher waist circumference.[466] Evidence from observational and intervention studies show that children who habitually consume SSBs have higher total energy intakes, which has been associated with higher adiposity.[467,469] However, these studies are not without limitations to do with adjustment for confounding factors, generalizability of study populations and experiment duration.[476] Additional RCTs are needed to provide corroborative evidence.

Observational research supports that children who consume more cow's milk tend to consume fewer SSBs, and vice versa.[470,471] A prospective cohort study of children aged 2-5 years revealed that milk and SSB consumption were inversely related, as were milk and fruit drinks.[472] Four-year-old children who consumed at least one serving of SSBs per day tended to consume lower amounts of milk.[473] One study found that children who were exposed to SSBs at a younger age were more likely to continue to consume them throughout childhood, in addition to consuming less cow's milk.[70] A cross-sectional study of 1134 children aged 2-5 years even specified that children who consumed whole fat milk regularly had the lowest intakes of SSBs and highest diet quality score.[6] Higher SSB intake has also been associated with less nutrient-rich dietary choices (i.e., fried foods and pizza) and higher overall energy intake, particularly among adolescents.[474]

Cow's milk and SSB consumption among children appears to change with age. One longitudinal study showed that compared to children aged 2 years, at 4 years of age children consumed less 100% juice but more carbonated beverages, and at 5 years of age children consumed less milk than at age 2 years.[475] Another prospective cohort study showed that

American children had lower intake of fruits, vegetables, cow's milk and breakfast, but higher SSB intake at age 15 years compared to at age 8 years.[476]

NHANES data show that children aged 0-5 years had 8% lower milk intake and 20% higher fruit juice intake when dietary information was compared between 1976 and 2006.[67] However, more recent NHANES data showed that between 2003 and 2012, energy intake from all beverages among young American children aged 2-5 years decreased.[464] To provide a broad view of American consumption trends, 67% of NHANES participants aged 6-11 years reported consuming SSBs in 1989-1991,[477] compared with 82% in 2003-2004, and 64% in 2013-2014.[478] Longitudinal population based data in Canada is not available.

Physiological effects of replacing cow's milk with SSBs have been evaluated among children in a few studies. A secondary analysis of an RCT of children aged 2-6 years revealed that children who replaced SSBs with cow's milk over a 1.5 year period had slightly lower zBMI (-0.07 zBMI per 100 g/day substitution, 95% CI -0.13 to -0.01, p= 0.04), while higher SSB consumption resulted in slight zBMI gain (+0.06 zBMI per 100 g/day SSB, 95% CI 0.001 to 0.12, p= 0.04).[479] A 16-week randomized controlled trial of 98 Chilean children with overweight or obesity aged 8-10 years evaluated the effect of replacing SSBs with flavoured milk. In this study, there was no evidence of different zBMI, fat mass or % body fat between groups, but children in the milk group showed evidence of higher lean mass following the intervention (+0.92 kg in milk group vs. +0.62 kg in SSB group, p= 0.04).[480] However, flavoured milk is by definition an SSB and 16 weeks is a relatively short trial period, limiting the relevance of these findings. Consistent findings were shown in a prospective cohort study of 623 American children aged 5-17 years, where children who consumed cow's milk regularly did not show evidence of zBMI change (+0.02; 95% CI –0.007 to 0.052; p= 0.13), whereas children who consumed SSBs had +0.05 zBMI (95% CI 0.022 to 0.079; p= 0.001) per daily SSB serving.[481] Intervention studies involving broader samples of children and comparing white milk to SSBs would clarify this relationship.

2.5.3.4 Dairy fatty acids

Dairy fatty acids have proposed benefits on metabolism and body composition, which are discussed in Section 2.1.6.1.3. To summarize, the specific types of fat provided by cow's milk, but few other foods, may offer protection against excess adiposity. Ruminant trans fatty acids (RP-TFAs) are produced by cattle rumen bacteria from polyunsaturated fatty acids (PUFAs), and have distinct effects from industrially produced trans-fatty acids such as those produced from hydrogenation of oils. RP-TFAs include trans palmitoleic acid, which may promote lower adiposity and better blood lipid profiles,[22,23,482] and conjugated linoleic acid (CLA), which RCT evidence has shown to have favourable effects on body fat in children.[27] CLA is suggested to lower adiposity[180,181] by increasing energy expenditure and lipid oxidation,[182] and reducing lipogenesis and appetite,[483] but the mechanisms are yet to be fully understood. Oleic acid, a prominent saturated fatty acid in cow's milk, may also have anti-inflammatory and anti-hypertensive effects and offer glycemic benefits such as moderating insulin response, though the magnitude of these produced by dairy foods alone is unknown.[147]

2.5.3.5 Vitamin D

In Canada, cow's milk is the main dietary source of vitamin D[484] due to Food and Drug Regulations which state that cow's milk must be fortified with approximately 100 IU of vitamin D per 250 mL cup.[485] TARGet Kids! observational research has revealed that 2-250 mL cups of cow's milk per day is enough for children to have sufficient serum 25-hydroxyvitamin D (25(OH)D) concentrations.[486] Vitamin D is a fat soluble vitamin and it is absorbed in the intestinal tract similarly to fat. Thus, the presence of fat in the intestine is believed to assist its absorption through the intestinal lumen and promote its secretion into the bloodstream.[216] Vitamin D is then stored in adipose or liver tissue.[405] The ideal amount or type of fat for optimal vitamin D absorption, as well as maintenance of sufficient serum 25-hydroxyvitamin D levels, has not been determined. Two studies revealed that adults who consumed a vitamin D supplement with a fat-containing meal had higher serum 25(OH)D than those who consumed a supplement with a lower fat or fat-free meal.[216,487] However, another study showed no evidence of a difference between the effect of vitamin D-fortified skim (0.1% fat) milk, whole milk and corn oil on toast on serum 25-hydroxyvitamin D.[488] A TARGet Kids! observational study which included 2745 children showed that those who consumed whole cow's milk had 5.4 nmol/L higher 25(OH)D concentrations than those who consumed 1% cow's milk, and 0.72 lower zBMI.[16]

Several observational studies have identified an association between higher adiposity and lower 25-hydroxyvitamin D.[31,34,36,401,402] Among 3381 Canadian children aged 6-17 years, 25(OH)D <50 nmol/L was associated with an OR for overweight or obesity of 2.19 (95% CI 1.46 to 3.28) for males and 1.39 (95% CI 1.05 to 1.84) for females, after adjustment for clinically relevant covariates (p values not reported).[489] These findings were similar to a study involving 2,492 American children aged 6 to 18 years who participated in NHANES. Higher serum 25(OH)D concentrations were associated with lower waist circumference (WC), waist-to-height ratio, BMI, triceps skinfold thickness, and percent body fat measured using dual x-ray absorptiometry in the 2005-2006 NHANES cycle.[490] Low vitamin D levels in children has been associated with higher screen time and lower physical activity,[491] higher serum triglycerides[33] and CRP[492] and lower HDL concentrations,[493] as well as insulin resistance.[494] It has been hypothesized that excess adipose tissue renders vitamin D unavailable due to its fat soluble properties.[404] High amounts of body fat may limit vitamin D's accessibility in serum for cells, bones and other tissues.[404,405] Another suggested mechanism is that low levels of vitamin D in the blood may stimulate a rise in parathyroid hormone, which causes an influx of calcium into adipocytes, where it induces lipogenesis.[37,396,407] Other reasons for lower vitamin D among children with higher adiposity may include limited time spent outdoors exposed to sunlight,[491] lower parental socioeconomic status or education leading to lower use of vitamin D supplements,[495,496] or diets which replace dairy foods with nutrient-poor foods.[418,497]

2.5.3.6 Reverse causality

Reverse causality, when the assumed directionality of a causal relationship is actually reversed, is a hypothesized explanation for the observed relationship between cow's milk fat and child adiposity. Rather than cow's milk fat having an effect on child adiposity, it is possible that parents of leaner children may provide higher cow's milk fat and parents of heavier children may provide lower cow's milk fat. However, little evidence exists to support the temporality and reasoning for these relationships.[39] One recent publication which aimed to understand if mothers participating in the Women, Infants and Children (WIC) program in California correctly perceived children's weights and provided leaner children with higher cow's milk fat and vice versa.[82] The researchers conducted surveys and qualitative interviews with 529 mothers of children aged 2-4 years. Results showed that 36% of the time, mothers tended to misclassify their child's weight as normal weight when children actually had obesity. A higher proportion of children who had underweight or normal weight consumed whole cow's milk relative to children with overweight or obesity, and a higher proportion of children with overweight or obesity consumed reduced fat cow's milk relative to those with under- or normal weight. However, these results may have limited generalizability for a number of reasons. The study population was mostly women of Hispanic ethnicity, who described whole milk as a traditionally healthy food for children, whereas reduced fat milk was commonly viewed as "watered down," incurring the perception that it was inferior to whole milk for child nutrition. Women in this study also viewed higher child adiposity as positive, which may be different than other perceptions of child overweight or obesity and elicit different behaviours (i.e., providing different foods to children).[82] The WIC program only provides reduced fat (1%) cow's milk to children who are not underweight or at risk of underweight,[498] which means that mothers of normal weight or heavier children would not have the option to provide whole milk if they were receiving cow's milk from WIC. Though the study objectives were to understand if mothers provided cow's milk fat depending on child adiposity, it was unclear whether mothers were asked this question directly.[82]

A prospective cohort study on the relationship between cow's milk fat intake and child adiposity between ages 2-3 years showed that children who consumed higher cow's milk fat at ages 2 and 3 years had lower adiposity, and that children who consumed reduced fat milk were not at a lower risk of excess adiposity compared to children who consumed whole milk. Adjusting for zBMI at age 2 and other relevant covariates, odds for incident overweight at age 3 were 0.95 (95% CI 0.58 to 1.55, p= 0.83) for skim/1% milk, and 1.04 (95% CI 0.74 to 1.44, p= 0.84) for whole milk drinkers.[7] They attempted to account for reverse causality by conducting a sensitivity analysis of only children who were had normal weight (zBMI -2 to 1). Although the sample size was smaller, there remained evidence of a relationship between higher cow's milk fat and lower child adiposity but it was weaker than the analysis involving all participants. Parents who were concerned about excess adiposity may have changed their child's milk fat intake, or possible effects of cow's milk fat may have been different for children with underweight or overweight. Further research is needed to understand these complex relationships.

2.6 Patient oriented research

Patient oriented research aims to prioritize the perspective of patients and families to answer relevant questions and provide care tailored to them. This approach asserts that patients and families be actively and meaningfully engaged throughout the entire research process.[499] Engaging parents as partners in research may be especially important when conducting studies on children's health, as parents make decisions to support healthy nutrition and lifestyle habits on their family's behalf. Parent perspectives to determine the relevance of research topics and feasibility of interventions are key to understanding child health interventions that hold potential for real-world impact.[500] The Strategy for Patient Oriented Research (SPOR) was developed by the Canadian Institute of Health Research (CIHR) to facilitate Canadian partnerships between researchers, healthcare providers, policymakers and patients and their families.[501] The SPOR encourages the inclusion of patients and families in all stages of study conduct, from formulating the research question to developing knowledge translation strategies and disseminating results. An overall objective of SPOR is to conduct research that is meaningful to patients and families, which maximizes applicability of research findings to clinical practice and the lives of patients.[501]

Due to the novelty of this field and diversity of settings, patient groups and objectives, patient engagement models vary. Typical frameworks include generalized spectrums or stages of patient involvement and are adapted to unique research environments. SPOR has developed a generic patient engagement framework, which provides overarching guiding principles:

inclusiveness of a diverse patient group, support for patients and families so they are able to meaningfully engage in all aspects of the research process, mutual respect for expertise, knowledge and experience of all members of the research team, and co-build, meaning patients and researchers work together to create a research process that answers meaningful research questions but also is a mutually beneficial process to engage in together.[499] Many patient-oriented research frameworks are adapted from the International Association for Public Participation's model for patient engagement,[502] which progresses through levels of low to high patient engagement. Levels include informing patients about research through websites or print media; consulting patients using focus groups or surveys to relay patient perspectives back to the research team; involving patients in workshops, forums, or panel discussions to provide a live voice for the patient perspective; collaborating with patients by designating roles such as patient committees or patient experts as a sustained member of the research team; and empowering patients to advocate for themselves in diverse settings such as conferences, citizen juries, or educating fellow patients about patient oriented research.[502]

Barriers to patient engagement often include perceived or real tokenism, where patients' perspectives may not reach the overall conduct of research but presence is viewed positively or used to meet a requirement.[503] As patient engagement often requires funding, child care, and operational support, considerable planning and resource allocation is required.[504] Patient partners perceive that they require literacy, social capabilities and confidence to engage with medical professionals and academics.[505] Providing guidance and education around health literacy, story-telling, and patient oriented research foundations is an important but underdeveloped and infrequently taken step when engaging patient partners.[500] Patient partners require compensation, resources to participate (e.g. childcare, transportation, translation services, online communication platforms for remote access), training and feedback highlighting their contribution to the project.[499] Investments such as these can facilitate meaningful, trusting and longstanding relationships, which justify the investment researchers make in patient oriented research. Researchers can also encounter homogeneous patient volunteers who have the time, willingness, and resources to attend patient meetings and contribute to research tasks as needed.[505,506] This can be problematic where evidence-based health interventions may be intended for people of all communities, but individuals with certain resources, priorities and social determinants of health have contributed to the intervention study design.[507] Homogenous patient partners also pose a problem for creating and executing knowledge translation activities because study results may not reach communities who are most in need.

Though the broader impact of patient oriented research is not fully described, various tools are available for patient oriented researchers to assess their own patient engagement efforts and receive feedback from patient partners.[508] Examples of assessment and evaluation tools include the Patient and Public Engagement Evaluation Tool (PPEET)[509] and the Guidance for Reporting the Involvement of Patients and the Public (GRIPP2) checklist.[510] Though evaluation tools are often tailored to specific patient populations, research settings and objectives, the high number of available tools has led to difficulty in comparing outcomes across settings or disciplines. Poorly adaptable design and lack of rigour in tool development has been cited as an overall weakness of patient engagement assessment tools.[511] Patients and members of the public were not always consulted in the creation of such tools, and results generated by them are infrequently reported back to participants.[508] A transferable, reliable, validated and collaboratively designed tool is needed to evaluate patient oriented research based on evidence and key stakeholder input.

Due to patient oriented research being relatively new, evaluation of its impact on patient outcomes, healthcare delivery, accessibility and quality, and public access to study findings have been limited thus far. A small body of literature suggests that patient participation in research leads to higher acceptability and accessibility of health services, and higher participant recruitment and retention rates in studies.[506] The interpretability, accessibility and relevance of research findings also have been found to be higher when patients are engaged in the research process from the start.[505,506] However, literature guiding researchers in identifying and recruiting patient partners, educating and engaging patients in various stages of research projects, and identifying which tasks may benefit most from patient engagement is limited or non-existent.[506] Best practices and evidence-based guidelines for patient oriented research have yet to be established.[504] Institutional guidance, educational resources and training opportunities, funding, and greater patient awareness for patient engagement opportunities would help researchers to develop meaningful collaborative relationships with patients,[506] which has been identified as a key facilitator of patient oriented research.[512]

2.7 Trials within Cohorts (TwiCs)

Randomized controlled trials have long been regarded as the "gold standard" method to determine the efficacy of an intervention. However, RCTs to evaluate nutrition interventions, especially in children, pose challenges such as limited applicability of highly controlled interventions to everyday life, small and poorly representative samples, and low adherence to intervention or control conditions.[513,514] In addition, traditional RCT methods have a number of limitations that have hindered their usefulness and inflated their cost. These include demand for time and resources presented to clinicians and participants, low generalizability, and lack of long-term outcomes, resulting in a constant need for replication.[515] Innovative clinical trial (ICT) designs have been developed to modify traditional RCT methods to lower cost, improve time efficiency, and increase the generalizability of results. Trials within Cohorts (TwiCs) is one type of ICT.

TwiCs trials leverage a large prospective cohort study to increase efficiency and overcome limitations of traditional clinical trials (see Table 6).[515] TwiCs trials function by randomizing eligible individuals within a cohort study to be offered an intervention or receive usual care, and using existing cohort study mechanisms to measure routinely collected outcomes in both groups. At the time of cohort study enrolment, patients consent to be randomized for TwiCs trials. Patients randomized to the intervention group are offered the intervention similar to how a therapy or treatment may be offered in routine care. Patients randomized to receive usual care serve as controls, allowing a true baseline to which outcomes can be compared.

In traditional RCTs, participants are informed about interventions that they may not receive since treatment allocation is determined by chance. Participants who are randomized to control groups or usual care may experience disappointment and be more likely to drop out of the study.[516] Participation in shared decision-making, which is customary in 21st century healthcare, is difficult to achieve resulting in a major barrier to participation – particularly for children. In TwiCs trials, this barrier is overcome by seeking trial specific consent only from participants who are randomized to the intervention group, replicating the consent process that occurs in routine clinical care. In other words, patients are approached with a known intervention and provided with information at the moment when they need it so they can accept or refuse to participate based on the knowledge of what they will receive. Control group participants, who receive standard of care (and with no additional measures outside of those routinely collected through the cohort study), are not approached for trial specific consent because they have already consented to participate in the cohort study. This approach is considered patient-centred because participants are provided with information relevant to them. It is intended to lower participant anxiety, reduce confusion about treatments they may not receive, and appropriately discuss the risks involved with a known intervention.[516]

Multiple advantages differentiate TwiCs trials from traditional RCTs including:

1) Lower Cost. Eligible participants are randomized to the intervention or the control group within the overarching cohort study, obviating the need for trial specific recruitment mechanisms. Further, all baseline and outcome measurements are already being conducted through the cohort study, resulting in additional cost savings.
2) Efficient. Recruiting participants into clinical trials is notoriously challenging. In TwiCs trials, randomization will occur within the cohort, where participants have already agreed to participate in research, reducing a major recruitment barrier. Considerable time normally needed for developing recruitment and data collection systems is also unnecessary, since data collection mechanisms in the cohort study are used for all measures in TwiCs trials.
3) Patient-Centered. In traditional RCTs, participants are informed about interventions they may not receive since treatment allocation is determined by chance. Participants cannot, therefore, participate in the shared decision-making process that is customary in 21st century healthcare. Since all participants have agreed to participate in cohort research, additional consent is only sought from participants who are randomized to the intervention group replicating the consent process that occurs in routine practice and eliminating a major barrier to clinical trial participation. Clinicians provide participants with information they need, at the moment they need it, with consent sought for a known

intervention. Control group participants, who will receive standard of care—with no additional measures outside of those routinely collected through the cohort study—will not be approached for additional consent.

Table 6. Limitations of current RCT designs and advantages of TwiCs designs

	Limitations of traditional RCTs	Advantages of TwiCs designs[515,517]
Cost	High cost of recruitment and follow-up particularly for controls who receive no intervention	Lower cost because recruitment and outcome measurement are funded by the cohort study; no additional cost for controls
Recruitment	Low numbers of participants particularly for children where outcomes are rare	Cohort with participants who have agreed to participate in research reduces barriers to trial recruitment
Consent	Patients undergo informed consent that often undermines participation	Mimics 'real-world consent' where participants are informed of the treatment they will receive
Follow-up	Short term follow-up of important outcomes	Ongoing outcome measurement in the longitudinal cohort ensures long-term follow-up of outcomes
Patient preferences	Little incentive to remain in trial if randomized to the standard of care group	All patients participating in the trial receive an intervention
Treatment comparisons	Meta-analysis of RCTs challenging due to heterogeneity in populations / outcomes	Can compare between competing interventions because of harmonized populations and outcome measurement
Shared resources	New RCT mechanisms set up for each trial	Multiple RCTs can occur concurrently with different children maximizing efficiency through shared resources

TwiCs trials also face challenges. Due to the pragmatic nature of TwiCs trials, it can be difficult to ensure interventions are correctly and consistently delivered, and collect adherence or compliance information among patients without adding to routinely collected outcomes or disrupting usual care. TwiCs are limited to unblinded studies since healthcare providers and patients must be aware of the intervention that is being offered. Contamination (participants receiving the opposite intervention or treatment to which they were assigned) may occur, especially where clinician preferences differ. However, participants in the control group are unaware of their allocation status, which may result in lower risk of cross-over, attrition and reporting bias among control patients. Compliance may be lower in TwiCs trials compared to traditional RCTs due to the timing of randomization, because consent is often provided much before randomization and offer of intervention. Individuals in the intervention group may refuse the intervention when the time of delivery arrives. When following an intention-to-treat protocol, this may dilute the overall observed effect of the intervention. Without structured follow up mechanisms additional to usual care, risk of attrition may be higher in TwiCs studies than traditional RCTs. TwiCs depend on a large, active cohort study, which is often unavailable and proposes challenges when infrequent outcomes are of interest.[518] Though some consider the TwiCs consent procedure to be transparent to patients, others have argued that participants who receive usual care and serve as controls in TwiCs studies should still be notified that their care was determined by random chance even when experimental treatments are not part of standard care.[519]

TwiCs are becoming more popular among researchers who have access to cohort studies, predominantly in Europe where large active cohort studies are relatively common. Though traditional RCTs and TwiCs face distinct challenges, there may be a unique role for TwiCs studies where large cohorts exist and have an existing framework to introduce highly efficient, pragmatic and generalizable trials. TwiCs methods have the potential to produce evidence that is relevant to patients and healthcare providers and at considerably lower cost and time than traditional clinical trials.

2.8 Comparative effectiveness research

Clinical practice guidelines are often based on consensus opinion or low-quality evidence.[520] Often, the high-quality evidence available to clinicians does not represent diverse patient populations, leading to uncertainty about benefits and risks patients will experience with the evidence-based intervention. According to the US Institute of Medicine, comparative effectiveness research (CER) aims to "assist consumers, clinicians, purchasers, and policymakers to make informed decisions that will improve health care at both the individual and population levels."[521] CER aims to engage both the clinician and patient in decision making in healthcare.[522] CER trials are considered pragmatic, in contrast to explanatory studies which are highly controlled and can be challenging to apply results to usual care settings. This type of research emerged from difficulty applying RCT evidence to everyday healthcare due to limited applicability to diverse patient populations, novel interventions not supported in routine care, and artificial research environments which cannot be mimicked.[523] Pragmatic trials typically take place in usual care environments, incur relatively low burden on participants, have wide inclusion criteria, and aim to include patient-relevant outcomes.[524] Comparative effectiveness research not only seeks to determine the most effective intervention of those being compared, but it also incorporates patient preferences and acceptability of interventions in practice.[523] In this way, CER focuses on the effectiveness of an intervention, rather than efficacy, as explanatory trials usually seek to do.[523] CER tends to measure outcomes, risks, and benefits that are relevant to patients: how well the intervention addresses symptoms, morbidity, or mortality; the safety of the intervention; lifestyle improvements offered, including measures such as quality of life and Patient-Reported Experience Measures (PREMs);[525] and cost of treatment.[523] As CER usually takes place embedded within health care settings where patient diversity is rich, it does not incorporate stringent exclusion criteria which are common to explanatory trials. In turn, results are considered to be more generalizable to clinical care, and may allow evaluation of which interventions work best for specific patient groups.[522]

While CER is a promising methodology to improve healthcare interventions, it carries some limitations. “Real-world” settings where CER takes place may have different characteristics in different institutions, countries or care environments. Patient preferences may also vary between studies, limiting generalizability of results across diverse populations.[526] CER can place extra responsibilities on healthcare providers to participate in research which may negatively impact the quality of care and quantity of time available to spend with patients.[527] CER studies often require relatively large sample sizes in order to detect clinically relevant differences between similar interventions, which can be challenging to attain.

2.9 Modified consent in clinical trials

Comparative effectiveness clinical trials often involve less risk than typical RCTs because they compare interventions which are already part of standard healthcare. Such interventions are either already offered, or do not carry additional risks to usual care, and one low-risk intervention should not be preferable over another to a reasonable person.[528] Studies testing low-risk interventions often do not cause greater risk to participants than everyday care. Several investigators have argued that the informed consent for these low-risk interventions be consistent with the consent process that occurs during usual healthcare, as opposed to typical consent processes for research studies.[528-530] A modified consent process has been advocated for these trials to reflect the true nature of risk involved, maintain a “patient-centred” approach, and efficiently gather consent for the specific intervention being offered.[529,531] Modified consent procedures are also helpful to minimize the potential for participation bias in studies of usual care interventions. Studies which seek to understand how typical patients respond to usual interventions and create evidence directly applicable to healthcare provision may be hindered by lengthy and impractical consent processes, which would not be a part of usual care.[530,532]

Informed consent is an essential component of health research which protects the rights and well-being of patients.[533] From the introduction of the informed consent process, consent procedures for studies which expose participants to a vast spectrum of risks have been the same. They provide individuals with the same amount information, in the same manner, regardless of the risk involved.[534] Though this is a well-intentioned process that is necessary and informative in many contexts, the result is that participants in low-risk studies are provided with information disproportionate to the degree of risk they are asked to incur. For low risk trials, the consent process has become burdensome, ritualistic and incomprehensible to research participants.[535] As a result, eligible people may misunderstand the degree of risk involved and decline to participate in research due to overwhelming, intimidating and inaccessible consent processes.[536] Lengthy consent forms may cause patients who are most in need of interventions to be excluded from studies due to time constraints or high perceived effort to complete the process,[530] leading to low recruitment and poorly generalizable results.[537]

In a 2014 survey of 1,095 American adults, 97% of respondents agreed that health interventions should be evaluated, but 73% perceived that taking part in health research, regardless of invasiveness or potential for harm, incurs additional risk. In this survey, 78% of respondents indicated that they would like to be asked permission before participating in any medical research, but consent could be oral or written.[538] Other surveys about consent for health research among adults have had similar findings.[539,540] In Europe, there appears to be willingness to participate in pragmatic RCTs for low-risk interventions without providing consent (39% of

Spanish respondents in one survey), but views on potential alternative consent methods (i.e., verbal consent) and ways to inform participants of waived-consent trials are varied.[541,542]

Proportionate consent is a modified consent procedure introduced to clinical trial methodology by the National Health Service (UK).[531] Through the proportionate consent process, consent is obtained in a way that is commensurate to the risks and benefits of participating in the particular study, such that low-risk studies of usual care interventions have shorter and less onerous consent processes than studies of higher-risk interventions. In all situations, participants are informed of the nature of the study, the material risks, benefits, and alternatives, and are provided adequate time to consider participation relative to factors such as the type of research being conducted, the setting and duration of the study, and potential for harm. Through the proportionate consent process for low risk studies, this information is often communicated verbally, similar to the way healthcare treatments are offered in standard healthcare.[531] Most often, proportionate consent is used in unblinded trials and is ideally suited to TwiCs trials where participants are provided with concise and relevant information at the moment they need it.[516,529] If adopted more widely, proportionate consent may offer investigators an efficient, effective and patient-centred approach to consenting participants to low-risk research.

2.10 Summary of literature review

Cow's milk is a nutrient-rich source of carbohydrates, protein, fat, and micronutrients, and has been consumed by Canadian children for over a century. Consensus-based dietary guidelines suggest that children aged 9 months to 2 years consume whole fat cow's milk, and children older than age 2 years transition to reduced (0.1-2%) fat cow's milk to reduce the risk of overweight or obesity. Evidence supporting this guideline dates to the 1990's which suggests reduced fat milk is safe for children to consume, but does not support that it is effective in lowering the risk of overweight or obesity.

Cow's milk has been shown to provide children with nutrients which support growth and development. Cow's milk fat may be one factor that explains conflicting evidence about the relationship between cow's milk consumption and excess childhood adiposity. Several observational studies have identified that higher cow's milk fat intake is associated with lower adiposity in children, but no interventional evidence is available. Given that the majority of Canadian children consume cow's milk on a daily basis, high quality evidence is needed to inform nutritional recommendations about cow milk consumption for children.

Randomized controlled trials are considered the gold standard of health research. However, traditional RCT methods have limitations which reduce their efficiency, inflate costs and impair the generalizability of results. Innovative clinical trials such as Trials within Cohorts are new methods which aim to overcome challenges to traditional RCTs and narrow the gap between highly controlled interventional research and everyday healthcare. This is especially important in nutrition research for children where applicability of interventions to healthcare practice is limited. A pragmatic randomized controlled trial to determine the optimal cow's milk fat for child growth, development and nutrition is needed.

CHAPTER 3: COW'S MILK FAT AND CHILDHOOD OVERWEIGHT: A SYSTEMATIC REVIEW AND META-ANALYSIS

3.1 ABSTRACT

Background. The majority of children in North America consume cow's milk daily. Children over age 2 years are recommended to consume reduced (0.1-2%) fat cow's milk to lower the risk of obesity.

Objective. To evaluate the relationship between cow's milk fat consumption and adiposity in children aged 1-18 years.

Design. EMBASE (Excerpta Medica Database), CINAHL (Cumulative Index to Nursing and Allied Health Literature), Medline, Scopus, and Cochrane Library databases from inception to August 2019 were used. The search included observational and interventional studies of healthy children aged 1-18 years were which described the association between cow's milk fat consumption and adiposity. Two reviewers extracted data, using the Newcastle Ottawa Scale to assess risk of bias. Meta-analysis was conducted using random effects to evaluate the relationship between cow's milk fat and risk of overweight or obesity. Adiposity was assessed using body mass index z-score (zBMI).

Results. Of 5682 reports identified by the search, 28 met inclusion criteria: 20 were cross-sectional and 8 were prospective cohort. No clinical trials were identified. In 18 studies, higher cow's milk fat consumption was associated with lower child adiposity and 10 studies did not identify an association. Meta-analysis included 14 of the 28 studies (N=20,897) which measured the proportion of children who consumed whole vs. reduced fat milk and direct measures of overweight or obesity. Among children who consumed whole (3.25% fat) vs. reduced fat (0.1 to 2%) milk, the odds ratio of overweight or obesity was 0.61 (95% CI 0.52 to 0.72, $p < 0.0001$), but heterogeneity between studies was high ($I^2 = 73.8\%$).

Conclusions. Observational research suggests that higher cow's milk fat intake is associated with lower childhood adiposity. International guidelines which recommend reduced fat milk for children may not lower risk of childhood obesity. Randomized trials are needed to determine which cow's milk fat minimizes risk of excess adiposity.

3.2 INTRODUCTION

Childhood obesity has tripled in the past 40 years with nearly 1 in 3 North American children now overweight or obese.[1,346,543] Over the same period, consumption of whole fat cow's milk has halved.[68] The American Academy of Pediatrics and the Canadian Pediatric Society recommend that children switch from whole fat cow's milk (3.25%) to reduced fat cow's milk (0.1 to 2%) at 2 years of age to limit fat intake and minimize the risk of childhood obesity.[53,304] European,[55] British[54] and Australian[56] health authorities have provided similar recommendations. Healthcare providers[544] and families[545] frequently follow this guideline, and school and child care nutrition policies[546-548] often reflect them. Since 1970 whole cow's milk availability has dropped by 80% in North America, whereas reduced fat milk purchases have tripled.[62,549]

Given that cow's milk is consumed daily by 88% of children aged 1 to 3 years and 76% of children aged 4 to 8 years in Canada[58] and is a major dietary source of energy, protein and fat for children in North America,[58,64] understanding the relationship between cow's milk fat and risk of overweight or obesity is important. Systematic reviews, narrative reviews and meta-analyses on the relationship between total dairy consumption and child adiposity have had conflicting findings (see *Appendix 8.2: Table 1*). According to these studies, higher cow's milk intake in children is associated with taller height and better bone and dental health.[223,246,247] Although these studies evaluated total dairy consumption, they did not take into consideration cow's milk fat specifically. The objectives of this study were to systematically review and meta-analyze the relationship between whole fat (3.25%) relative to reduced fat (0.1 to 2%) cow's milk and adiposity in children.

3.3 METHODS

A systematic review and meta-analysis of the literature was conducted. The study was designed according to the PRISMA-P guidelines[550] and registered as a PROSPERO systematic review and meta-analysis (registration number: CRD42018085075).

Inclusion Criteria. *Types of studies.* Studies included in the search were original works published in English in a peer-reviewed journal. Cross-sectional, cohort, case-control, longitudinal studies, as well as intervention trials, both controlled and not controlled, were included in the search strategy. There were no restrictions on date or length of follow up.

Population. Studies which included healthy children 1 to 18 years of age with at least ten human subjects were considered. Studies that examined undernourished or diseased populations (other than asthma) were excluded.

Exposures. The primary exposure was cow's milk fat, categorized as skim (0.1% fat), 1% fat, 2% fat, or whole or homogenized (3.25% fat). Measures of exposure included food frequency questionnaire (FFQ), multi-day food record, 24-hour food recall, or any other validated or non-validated dietary measurement tool. Dietary pattern analyses were not included.

Outcomes. The primary outcome was childhood adiposity. These measures included body mass index (BMI) z-score, BMI, weight for age, body fat mass, lean body mass, waist circumference, waist to hip ratio, body fat percentage, skinfold thickness and prevalence of overweight or obesity defined by World Health Organization (WHO),[344] Center for Disease Control (CDC),[551] or International Obesity Task Force (IOTF)[338] cut-offs. When sufficient information was not available in the full text publication, study authors were contacted by email to obtain additional data.

Meta-analysis. Meta-analysis included studies that reported the number of children who consumed whole (3.25%), 2%, 1% or skim (0.1%) milk regularly (a-priori defined as typically, daily, or ≥ 4 times per week), as well as the number of children from each of these groups who were classified as either healthy weight, or overweight or obese (overweight and obese were included as one category) assessed using BMI standardized using WHO,[344] CDC,[551] or IOTF[338] criteria.

Search methods. A comprehensive search strategy was developed by a research librarian (NT) with expertise in systematic reviews. From inception to August 2019, EMBASE, CINAHL, Medline, Scopus, and the Cochrane Library were searched on March 23, 2018 and updated on August 2, 2019 using Medical Subject Headings (MeSH) and keywords (see Online Supporting Material for search strategies).

Data extraction, management and analysis

Study selection. To evaluate study eligibility two reviewers (MA and SV) independently reviewed study titles, abstracts, and full texts if needed. Both reviewers applied inclusion and exclusion criteria and differences were examined and resolved by consensus, which was achieved 100% of the time. Full text manuscripts were retrieved for potentially eligible studies and reviewed. Characteristics of included full text studies were summarized.

Data extraction. Two reviewers (MA and SV) extracted data from eligible studies using standardized data extraction tables adapted from the Cochrane Data Extraction Template.[552] Differences were resolved by consensus 100% of the time.

Data management. Covidence[553] software was used to select studies, review results and resolve discrepancies between reviewers. All included study records were kept in spreadsheet format.

Data synthesis. Studies included in the analysis were described according to a standardized coding system which captured key elements of each study including descriptors of the study setting, population size and age (mean and range), exposure or intervention, comparator group, method of data collection, outcome measures, type of analysis, and results.

Risk of bias and study quality assessment

Risk of bias was assessed using the Newcastle Ottawa Scale (NOS)[554] for nonrandomized analyses, which expresses the risk of bias on a numerical scale ranging from zero to nine; scores of seven and above are considered low risk.[554] NOS criteria can be found in Table 8. The NOS guided review included an examination of participant selection, comparability of children consuming whole or reduced fat milk, and exposure and outcome measure ascertainment.[554] To allow sufficient follow-up time for a meaningful change in adiposity to occur, the minimum acceptable follow-up time was pre-specified as one year. Study comparability, defined as whether studies adjusted for similar confounding variables, was specified *a priori* as studies that adjusted for important characteristics including: birth weight or baseline weight (for prospective cohort studies), milk volume consumed, and parent BMI. Studies that adjusted for each of these factors were awarded two points, whereas 1 point was allocated if adjustment was performed using four or more other covariates. Reports were assigned 1 point for ascertainment of exposure only when structured interviews or medical records were used for data collection measure.[554] Risk of bias was assessed by two reviewers (MA and SV) and consensus was achieved 100% of the time.

Statistical Analysis. For each study, participant information, design and results were summarized. We derived crude odds ratios and extracted adjusted odds ratios, whenever available, for overweight or obesity among children who consumed whole (3.25%) milk, compared to children who consumed reduced fat (0.1% to 2%) milk regularly. A random effects model based on the restricted maximum likelihood estimator was decided *a priori* and used to separately pool crude and adjusted odds ratios of overweight or obesity. Each study was included as a random effect to account for between-study variation in this model. Sensitivity analyses were performed using the Knapp-Hartung method[555] and inverse-variance weights. Since prospective cohort studies may reveal different relationships than cross sectional studies, we performed a subgroup analysis according to study design. Additionally, we analyzed studies in subgroups according to risk of bias (high vs. low) and age (1-5 years, 6-11 years, and 12-18 years). Subgroup analyses were accompanied by tests for interaction between each subgroup and the main effect from the random-effects meta-regression, by using an interaction term in meta-regression models for study design (cross sectional vs. prospective cohort), risk of bias (high vs. low), and age group (1-5 years, 6-11 years, and 12-18 years). Heterogeneity across included studies was estimated using the I^2 statistic.[556] Heterogeneity was considered low (<40%), moderate (40-60%) or high (>60%).[143] Publication bias was assessed using a funnel plot and Egger's test.[557]

Finally, we conducted a dose-response meta-regression to quantify the association between percentage of fat in cow's milk consumed and the odds of overweight or obesity. Only studies that reported group-specific odds for ≥ 3 types of cow's milk fat were included in this analysis. For the dose-response analysis, we first used a fixed-effect approach to estimate the dose-response relationships within each study. Then, we used a random-effects approach to combine across studies the dose-response estimates that were generated in the first step for each study[558] to obtain regression coefficients, and their respective standard errors. R software version 3.2.2[559] was used for all analyses, using the 'metafor' package.[560]

3.4 RESULTS

The database search identified 5682 potentially eligible studies. After exclusion of duplicates (n=1861), 4001 reports underwent title and abstract review. Studies that did not meet inclusion criteria (n=3915) were removed resulting in 86 published studies which underwent full text review (Figure 1). Reasons for exclusion included wrong exposure, wrong outcome, wrong patient population, dietary pattern analysis only, or wrong study design such as case reports or editorials. Twenty-eight studies met all inclusion criteria. Of these, 20 were cross-sectional and 8 were prospective cohort studies (See Table 7 for study characteristics). No interventional studies were identified. Most studies (n=23) compared whole milk (3.25% fat) to reduced fat milk consumption (0.1%, 1% or 2% fat). Four studies[561-564] compared whole and 2% milk to 1% and skim milk. One study compared whole to 2% milk.[565]

Nineteen studies used zBMI, 4 prospective cohort studies used % body fat change and 5 studies used overweight or obesity categories as the primary adiposity outcome. Three studies used 2008 WHO[344] growth standards, 14 studies used 2000 CDC[551] growth standards, 7 used 2000 IOTF[338] growth standards, and 4 studies either did not specify or used other standards for zBMI measurement.

Eighteen[4,6,8-11,82,561,563,564,566-573] studies reported that higher cow's milk fat was associated with lower child adiposity. Ten studies[39,562,565,574-580] reported no association between cow's milk fat and child adiposity.

Risk of bias assessment

Risk of bias using the Newcastle Ottawa Scale suggested that 1 of 8 prospective cohort studies and 0 of 20 cross-sectional studies were low risk of bias (See Table 8). Common limitations which increased risk of bias included cross-sectional study design, non-standardized dietary assessments which were either study specific or not validated, lack of adjustment for clinically important covariates (including volume of milk consumed, parent BMI and child adiposity assessed prior to the outcome), and study duration too short to detect a meaningful change in adiposity (defined *a priori* as 1 year).[581]

Association between cow's milk fat and child overweight or obesity

Fourteen[4,7,9-11,82,563,567-570,573,579] studies met the meta-analysis inclusion criteria, 11 of which were cross-sectional and 3 were prospective cohort studies. All studies included in the meta-analysis compared whole (3.25% fat) milk to reduced (0.1% to 2%) fat milk consumption, allowing an odds ratio to be calculated. A total of 20,897 healthy children aged 1-18 years were included in the meta-analysis. Children were from 7 countries (USA, UK, Canada, Brazil, Sweden, New Zealand, and Italy). Anthropometric standards which were used to determine overweight or obesity categories included the WHO,[344] CDC,[551] or IOTF[338] growth standards in six, five and three studies respectively.

Crude analysis of all 14 studies revealed that among children who consumed whole milk vs. reduced fat milk, the pooled odds ratio for overweight or obesity was 0.61 (95% CI 0.52 to 0.72, $p < 0.0001$) (Figure 2). Heterogeneity measured by the I^2 statistic was 73.8% ($p<0.0001$). A sensitivity analysis using inverse-variance weights did not reveal different results. Subgroup analysis by study design revealed no significant interaction between cross sectional and prospective cohort studies ($p= 0.07$, *Appendix 8.2: Table 2*). For the 11 cross-sectional studies (n= 9,413), the pooled odds ratio of overweight or obesity was 0.56 (95% CI 0.46 to 0.69, $p= 0.0001$) and for the 3 prospective cohort studies (n= 11,484) it was 0.76 (95% CI 0.63 to 0.92, $p= 0.006$). Risk of bias (high vs. low) and age group were also not significant modifiers of the relationship between cow's milk fat and child adiposity (*Appendix 8.2: Table 2 and Figures 1-5*). Analyses of 5 studies[4,11,568-570] that reported adjusted odds ratios did not show differences between crude and adjusted estimates (adjusted OR= 0.53 (95% CI 0.44 to 0.63); crude OR= 0.55 (95% CI 0.46 to 0.66); see *Appendix 8.2: Figure 6*). Results of the sensitivity analysis using the Knapp Hartung method[555] to pool the 14 studies (crude OR= 0.62 (95% CI 0.52 to 0.73)) was similar to the main results (crude OR= 0.61 (95% CI 0.52 to 0.72)). Publication bias, visualized using a funnel plot (*Appendix 8.2: Figure 7*) was difficult to ascertain given high heterogeneity (I^2= 73.8%) and relatively low number of included studies.

The dose-response meta-analysis results are shown in Figure 3. Data were available from 7 studies[4,9,563,564,566,568,569] which included 14,582 children aged 2 to 11 years and demonstrated a linear association between higher cow's milk fat and lower child adiposity. For each 1% higher cow's milk fat consumed, the overall crude odds ratio for overweight or obesity was 0.75 (95% CI 0.65 to 0.87, p= 0.004, τ^2= 0.01, I^2= 64%).

3.5 DISCUSSION

This systematic review and meta-analysis has identified that relative to reduced fat cow's milk, whole fat cow's milk consumption was associated with lower odds of childhood overweight or obesity. The direction of the association was consistent across a range of study designs, settings, age groups and demonstrated a dose effect. Although no clinical trials were identified, existing observational research suggests that consumption of whole vs. reduced fat milk does not adversely affect body weight or body composition among children and adolescents. To the contrary, higher milk fat consumption appears to be associated with lower odds of childhood overweight or obesity.

Findings from the present study suggest that cow's milk fat, which has not been examined in pervious meta-analyses, may play a role in the development of childhood overweight or obesity. Several mechanisms have been proposed which may explain why higher cow's milk fat consumption might result in lower childhood adiposity. One theory involves the replacement of calories from less healthy foods, such as sugar sweetened beverages, with cow's milk fat.[20] Consumption of beverages high in added sugar have been associated with increased risk of overweight and obesity during childhood.[582] Other theories involve satiety mechanisms such that higher milk fat consumption may induce satiety through the release of cholecystokinin and glucagon-like peptide 1[445,583] reducing desire for other calorically dense foods. Another possibility is that lower satiety from reduced fat milk may result in increased milk consumption causing higher weight gain relative to children who consume whole milk, as observed in the study by Berkey et al.[39]

Cow's milk fat may offer cardiometabolic benefits. The types of fat found in cow's milk, including trans-palmitoleic acid, may be metabolically protective. Higher circulating trans-palmitoleic acid has been associated with lower adiposity, serum triglyceride concentrations and insulin resistance, and higher HDL cholesterol in several large adult cohort studies.[22,23,482] However, diets which replace dairy fat with unsaturated fatty acids may offer cardiometabolic protection.[584,585]

Confounding by indication and reverse causality[586] are plausible alternate explanations. Parents of children who have lower adiposity may choose higher fat milk to increase weight gain. Similarly, parents of children who have higher adiposity may choose lower fat milk to lower the risk of overweight or obesity.[6,9] The majority of children included in this systematic review were involved in prospective cohort studies, in which the potential for reverse causality is lower than cross sectional studies. Clinical trial data would have provided better evidence for the directionality of this relationship, however none was available. Results from these 11,484 children were consistent with the overall findings. Two of the included prospective cohort studies[7,39] attempted to address confounding by indication by adjusting for baseline BMI, one of which repeated the statistical analysis only among participants with normal weight BMI values with similar findings.[7]

This study had a number of strengths. The meta-analysis included a large, diverse sample of children from around the world. The number of potentially eligible studies was maximized by the comprehensive search strategy and contact with authors to obtain missing data. Also, study selection, data collection and risk of bias assessment were performed by two independent reviewers which improved accuracy and consistency. All studies included in the meta-analysis used trained individuals to obtain anthropometric measurements and weight status was standardized using growth reference standards (WHO, CDC and IOTF). Using meta-regression techniques, differences in study design, risk of bias, and age group were taken into account. Finally, a dose-response meta-analysis was conducted which demonstrated a linear relationship between higher cow's milk fat and lower child adiposity (Figure 3).

This study had a number of limitations. First, included studies were all observational. Only one study in this analysis was considered to have low risk of bias, and all studies in the meta-analysis had high risk of bias. Risk of bias included cross-sectional designs and lack of adjustment for clinically important covariates. For example, cow's milk volume was accounted for in only 11 of 28 studies in the systematic review and 5 of 14 studies in the meta-analysis. Adjustment for volume in future studies would allow for a clearer understanding of whether higher cow's milk fat protects against higher adiposity, or reduced fat cow's milk increases adiposity. However, among these studies, comparison of adjusted vs. crude odds demonstrated consistent findings. Residual confounding by variables not accounted for in the individual analyses is also possible, which is a common limitation for meta-analyses of observational studies. Heterogeneity was relatively high (I^2=73.8%) which may have been attributable to a variety of factors including varied methods of ascertainment of exposure and outcome, differences in study design and follow-up duration. While subgroup analyses of prospective cohort studies revealed comparable results to the overall meta-regression, these comparisons may not have had sufficient power to detect clinically meaningful differences. However, 11,484 children were involved in prospective cohort studies making large differences in effect size unlikely. Although only studies with standardized dietary measurements were included, measurement error was possible due to recall bias or lack of validation of dietary assessment tool. Error in adiposity measurement may also have introduced bias, though weights and heights were measured by trained individuals and standardized protocols were used in all studies included in the meta-analysis. Differences in adiposity measurement (i.e. body fat percentage, zBMI, BMI), and different growth standards may have contributed to heterogeneity. For example, use of the WHO rather than IOTF or CDC standards may have resulted in a greater proportion of overweight or obese children reported.[339] Future studies using WHO growth standards, which are believed to represent optimal child growth,[344] would help to minimize heterogeneity and overcome these limitations. Consideration for relevant outcomes such as cardiovascular risk should be included in future analyses to understand other effects of cow's milk fat. Publication bias was also possible as demonstrated by a funnel plot and Egger's test.

3.6 CONCLUSION

Observational evidence supports that children who consume whole milk vs. reduced fat milk have lower odds of overweight or obesity. Given that the majority of children in North America consume cow's milk on a daily basis, clinical trial data and well-designed prospective cohort studies involving large, diverse samples, using standardized exposure and outcome measurements, with long study duration would help determine whether the observed association between higher milk fat consumption and lower childhood adiposity is causal.

Table 7. Data Summary Table for Milk Fat and Child Overweight: A Meta-Analysis

Cross Sectional Studies						
Author, year	**No. children Age range Location**	**Exposure, method**	**Outcome**	**Variables adjusted for**	**Adjusted result**	**P value**
Acharya, 2011[571]	770 3-5 years USA	Frequency of low- or high-fat milk intake, 24-h recall and FFQ with trained interviewers	zBMI (CDC)	Energy intake	Reduced fat milk was positively associated with 0.52 (95% CI 0.29-0.75) higher zBMI. Children who consumed reduced fat milk were more likely to be OB (OR= 2.98 (95% CI 1.46-6.05)	0.03
Barba, 2005[10]	884 3-11 years Italy	Frequency of milk consumption by milk fat content, parent completed questionnaire	zBMI (IOTF)	Age, birth weight, parental OW/OB, parental education level, physical activity, frequency of consumption of the other groups of foods (dairy foods, fish, cereals, meat, fruit, vegetables, sweet beverages, snacks)	Whole milk was associated with 0.112 lower zBMI (95% CI -0.19 to -0.33). Children who consumed whole milk least often were more likely to be OW than those who consumed it most often (OR= 2.18, 95% CI 1.30-3.66)	0.005
Barbiero, 2008[573]	405 10-18 years Brazil	OW/OB (WHO)	Dietary habits, food intake by parent completed questionnaire	None	Reduced fat milk greater among children with OB. Whole milk: normal weight 91.7%,	0.08

					OW 89.7%, OB 61.1%. Skimmed milk: normal weight 8.3%, OW 10.3%, OB 38.9%	
Beck, 2017 [9]	135 3 years USA (WIC)	Milk fat, 24-h recall by trained research assistant	OW/OB (CDC)	Gender, maternal BMI, maternal education, maternal marital status, mother's preferred language, and mother's total years in the US	Children with severe OB had a lower intake of cow's milk fat and more likely to consume skim (0.1%) milk (OR= 0.89, 95% CI 0.81-0.97)	0.01
Charvet, 2019[564]	197 3-4 years USA (WIC)	Beverage intake, measured using a nutrition and sociodemographic characteristics questionnaire	BMI percentile (CDC), measured by trained Women, Infants and Children staff	None	A higher proportion of children with OW or OB consumed reduced fat cow's milk than children with under- or normal weight	0.014
Dodd, 2013[562]	2,314 6-18 years USA	Weight status (OW/OB), measured by field interviewers using standardized procedures (CDC)	Beverage consumption, child- and parent-completed 24-h recall interviews	NR	No significant differences in cow's milk fat and weight status. Normal weight elementary and middle school children were more likely to consume 2%/whole milk. Among high school children, OW/OB children were more likely to consume reduced fat milk (effect sizes NR)	NR
Eriksson, 2010[572]	114 8 years	Food intake, parent and child	BMI (IOTF)	None	Children who never/seldom consumed whole milk had a	BMI, <0.001

	Sweden	completed 24-h recall with registered dietitian			mean BMI of 17.7, whereas children who consumed 1 serving per day of whole milk had a mean BMI = 16.2, >1 serving per day mean BMI= 15.4. Overall difference of 2.3 BMI	
Gaylis, 2017[579]	598 13-19 years USA	Self-reported BMI, categorized into healthy, OW, obese (CDC)	Frequency of whole and low-fat milk consumption, child completed FFQ	None	No difference in cow's milk fat intake between weight categories (effect size NR)	NR
Kim, 2019[82]	529 3-4 years USA (WIC)	BMI percentile (CDC), measured by trained Women, Infants and Children staff	Cow's milk fat consumed, assessed during telephone interview	None	A higher proportion of children with OW or OB consumed reduced fat cow's milk than children with normal weight	<0.01
LaRowe, 2007[6]	1,334 2-11 years USA (NHANES)	Beverage intake patterns, interview by caregiver	BMI (CDC)	Age, sex, ethnicity, household income, Healthy Eating Index score, physical activity, birth weight	Among children aged 6-11 years, those who consumed whole milk had lowest BMI and higher healthy eating scores. BMI was significantly higher in the water, sweetened drinks, and soda patterns (adjusted mean BMI=19.9, 18.7, and 18.7, respectively) compared to the mix/light and whole milk patterns (adjusted mean BMI=18.2 and 17.8, respectively) (P<0.05)	BMI, <0.05; >85th percentile (both age groups), <0.0001

					Proportion of children aged 6-11 years with OW/OB: whole milk 22.1%, soda 35.2%, mix/light drinker 28%, water 42.6%, sweetened drinks 35.4% Proportion of children aged 2-5 years with OW/OB: whole milk 26.9%, mix/light drinker 15.0%, water 25.8%, fruit juice 19.6% In children aged 2-5, no significant association between milk fat content and BMI (effect size NR)	
Mazahery, 2018[11]	1,155 2-4 years New Zealand	Frequency and fat content of milk consumption (questionnaire)	BMI, measured by trained testers (IOTF)	NR	Higher odds of consuming reduced fat milk among OW/OB (OR= 1.74, 95% CI 1.20-2.54 for OW, OR= 1.48, 95% CI 0.73-3.01 for OB), compared to normal weight children	OW, <0.05; OB, >0.05
Milla Tobarra, 2014[575]	373 9-11 years Spain	Beverage intake, child-completed 24-h recall	BMI (IOTF)	Age, cardiovascular fitness	OW/OB children were less likely to drink whole milk than thin or normal weight children Thin girls consumed a mean 2.9 mL/kg/d more whole	Girls, 0.002; boys, 0.043

					milk than OW/OB girls; thin boys 2.8 mL/kg/d more whole milk than OW/OB boys	
Nelson, 2004[570]	451 2-4 years USA	BMI, measured by a medical provider (CDC)	Nutrition and sociodemographic characteristics	Race/ethnicity, age, sex, birthplace of the parent, fat content of milk consumed by children in family, fruit/vegetable consumption, exercise	Children who consumed whole milk were less likely (OR = 0.50, 95% CI 0.31-0.80) to be OW/OB	<0.01
Nilsen, 2017[569]	2,104 7-9 years Sweden	Food and beverage intake frequency, parent completed questionnaire	OW/OB (WHO)	Gender, parental weight status, parents' education level and area of living	Odds of being OW/OB were higher among those who consumed reduced fat milk (OR = 1.90, 95% CI 1.40-2.48) compared to those who consumed whole milk. Inverse association between odds of OW/OB and whole milk consumption (OR = 0.60, 95% CI 0.39-0.78)	0.001
O'Connor, 2006[574]	1,160 2-5 years USA	Beverage consumption, parent completed 24-h recall interview	BMI percentile	Age, ethnicity, gender, income, energy consumed, physical activity	No significant association between cow's milk fat and weight status (effect size NR)	NR
Papandreou, 2013[576]	607 7-15 years	Beverage intake 24-h recall x 3	BMI, OW/OB (IOTF)	Age, gender, income, energy	Cow's milk fat was not significantly associated	NR

	Greece	days by registered dietitian		intake, physical activity	with weight status (effect size NR)	
Ruxton, 1996[577]	136 7-8 years Scotland	Milk intake, 7 day food record by parents	zBMI	NR	No significant relationship between fat content or volume of milk and anthropometry or growth (effect size NR)	NR
Schroeder, 2014[578]	1,149 10-18 years Spain	Beverage consumption, 24-h recall by child	zBMI	Age, energy underreporting, mother's educational level, physical activity, television viewing, energy intake	Comparison between reduced fat and whole milk on zBMI not significant. For boys, OR= 1.21 (95% CI 0.95-1.56; for girls, OR= 10.4 (95% CI 0.79-1.37) for higher zBMI	Boys, 0.199; girls, 0.792
Tovar, 2012[568]	217 6-11 years USA	OW and OB prevalence (CDC)	Diet quality, parent completed questionnaire	Age, gender, race/ethnicity, state of residence, number of members in the household, family government assistance	OW (OR= 0.90, 95% CI 0.40-1.80) and OB children less likely (OR= 0.40, 95% CI 0.20-0.70) to consume whole milk than normal weight children	OW, 0.80; OB, 0.001
Vanderhout, 2016[4]	2,738 1-5 years Canada	Milk fat content consumed, parent completed FFQ	zBMI (WHO)	Age, sex, vitamin D supplementation, minutes per day of both outdoor free play and	Participants who consumed whole milk had 0.72 (95% CI: 0.68-0.76) lower zBMI score than children who consumed reduced fat milk	<0.0001

				screen time, milk and SSB volume consumed daily, maternal BMI, skin pigmentation, family income, maternal ethnicity, date		

Prospective Cohort Studies							
Author, year	**N, age range**	**Duration**	**Exposure**	**Outcome**	**Variables adjusted for**	**Adjusted Result**	**P value**
Berkey, 2005[39]	12,829 9-14 years USA	3 years	Dietary intake, self-administered FFQ	BMI (CDC)	Prior-year BMI *z* score, physical activity and inactivity, race or ethnicity, sex, age and maturational stage, height growth	Among boys, 0.027 higher BMI (95% CI 0.002-0.053) with every daily serving of 1% milk, and girls 0.021 higher BMI per daily serving of reduced fat milk (95% CI 0.001-0.04). BMI gains among children who consumed whole milk were not significant. Dairy fat (cheese, butter, etc.) was not significantly associated with BMI (effect NR)	<0.05, dairy fat NR
Bigornia, 2014 [567]	2,282 10-13 years UK	3 years	Dairy fat, parent assisted 3 day food records	Body fat %, BMI (IOTF)	Sex, volume of dairy intake, age, height, maternal education, maternal OW status, physical	Children who consumed the most whole fat dairy compared to the least whole fat dairy at age 10 and 13 had the lowest risk of excess fat mass (OR = 0.64, 95% CI 0.41-1.00), and a lower risk of OW (OR = 0.65, 95% CI 0.40-1.06) at age 13. High vs. low whole fat dairy	Fat mass, 0.03; OW, 0.24; BMI gains, <0.01. Reduced fat NR

					activity, pubertal stage, dieting at follow-up, baseline intakes of cereal, total fat, total protein, fiber, 100% fruit juice, fruit and vegetables, SSBs, dietary reporting errors at follow-up	consumption also had the smallest gains in BMI (2.5 kg/m^2 (95% CI 2.2-2.7) vs. 2.8 kg/m^2 (95% CI 2.5-3.0)). Reduced fat dairy associations with adiposity were not significant	
DeBoer, 2015[561]	8,950 4-5 years USA	1 year	Volume and fat content of milk, parent online interview	zBMI (CDC)	Sex, race/ethnicity, SES	Every 1% increase in milk fat was associated with 0.176 (95% CI -0.197 to -0.155) lower zBMI among 4 year olds and 0.139 lower zBMI (95% CI -0.173 to -0.105) among 5 year olds	<0.001
DuBois, 2016[580]	304 9-14 years Canada	5 years	Dietary intake, 2x24-h recalls by parent and child with registered dietitian	BMI (IOTF)	Each twin served to balance characteristics of other twin	Heavier twin boys consumed more whole milk and alternatives than their leaner twin; heavier girl twins consumed less whole milk than their leaner twin. Reduced fat milk consumption among girls was associated with a 0.32 higher BMI from age 9-14 years, whole milk did not have a significant relationship with BMI	<0.05

Huh, 2010[7]	852 2-3 years USA	1 year	Volume and fat content of milk consumed, parent completed FFQ	zBMI (CDC)	Age, sex, race/ethnicity, energy intake, non-dairy beverage intake, TV viewing, maternal BMI and education; paternal BMI, 2-year BMI z-score	Higher intake of whole milk at age 2 associated with −0.09 unit per daily serving, (95% CI −0.16 to −0.01) lower zBMI at age 3 Cow's milk fat intake not related to OW; ORs for OW at age 3 were 1.04 (95% CI 0.74-1.44) for whole milk, 0.91 (95% CI 0.20-1.34) for 2% milk, and 0.95 (95% CI 0.58-1.55) for 1%/skim milk	zBMI, 0.02 OR for OW: whole milk, 0.84; 1%/skim, 0.83
Noel, 2011[8]	2,245 10-13 years UK	3 years	Milk fat, parent- and child-completed 3 day food records	Body fat %	Age, sex, height, physical activity, pubertal status, maternal BMI, maternal education, dietary intakes of total fat, ready-to-eat breakfast cereal, 100% fruit juice, and SSB intake, calcium, total	At age 13, per daily serving of whole milk, a 1.32% lower body fat (95% CI -2.36 to -0.27) was seen. Longitudinal relationships were not significant	0.01

					energy intake, metabolic rate		
Scharf, 2013[563]	8,350 2-4 years USA	2 years	Milk fat, parent completed online questionnaire	zBMI (CDC)	Sex, race, SES, juice and SSB intake, number of glasses of milk daily, maternal BMI	Children who consumed reduced fat (skim/1%) milk had higher odds of OW (age 2 OR= 1.64, 95% CI 1.32-2.03; age 4 OR= 1.63, 95% CI 1.23-1.86) or OB (age 2 OR= 1.57, 95% CI 1.03-2.42; age 4 OR= 1.64, 95% CI 1.04-2.60) than those consuming whole/2% milk. Children who were normal weight at age 2 who consumed skim/1% milk more likely to become OW/OB at age 4 (OR= 1.57, 95% CI 1.03-2.42)	OW age 2, 4, OB age 4: <0.0001; OW age 4: 0.002; becoming OW/OB age 4: 0.04
Wosje, 2001[565]	51 1-2 years USA	1 year	Milk fat consumption at 12, 18 and 24 months, 3-day food record, parent completed	Weight, body fat change	NR	No difference in weight or body fat at 12, 18 or 24 months, or changes in anthropometry between children consuming reduced fat or whole milk (effect sizes NR)	NR

OW= overweight, defined by >85th percentile for BMI or >1 for zBMI, OB = obesity, defined as >95th percentile for BMI and >2 for zBMI [587]; FFQ= food frequency questionnaire; 25(OH)D= 25-hydroxyvitamin D; zBMI= Body Mass Index z-score; NR= not reported, SSB= sugar sweetened beverage, SES= socioeconomic status. Adiposity outcomes, where reported, were standardized according to WHO (World Health Organization), CDC (Centers for Disease Control), or IOTF (International Obesity Task Force). Shaded studies were those included in the meta-analysis.

Table 8. Risk of Bias - Newcastle Ottawa Scale[554] for Nonrandomized Studies

	Represent-ativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Outcome of interest not present at start	Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Duration sufficient for outcomes to occur (>1 year)	Adequacy of follow up of cohorts	Total	Overall risk of bias
Cross-sectional studies (20)										
Acharya, 2011[571]	X	X	X			X			4	High
Barba, 2005[10]	X	X			X	X			4	High
Barbiero, 2008[573]	X								1	High
Beck, 2017[9]	X	X	X		X	X			5	High
Charvet, 2019[564]	X	X	X			X			4	High
Dodd, 2010[562]	X	X	X			X			4	High
Eriksson, 2010[572]	X	X	X						2	High
Gaylis, 2013[579]	X	X							2	High
Kim, 2019[82]	X	X	X						3	High
LaRowe, 2007[6]	X	X	X		X	X			5	High
Mazahery, 2018[11]	X	X	X						3	High
Milla Tobarra, 2014[575]		X				X			2	High
Nelson,	X	X	X		X	X			5	High

2004[570]										
Nilsen, 2017[569]	X	X			X	X			4	High
O'Connor, 2006[574]	X	X	X		X				4	High
Papandreou, 2013[576]	X	X	X		X	X			5	High
Ruxton, 1996[577]	X	X				X			3	High
Schroeder, 2014[578]	X	X			X	X			4	High
Tovar, 2012[568]	X	X			X	X			4	High
Vanderhout, 2016[4]	X	X			X	X			4	High
Total low risk										**0**
Prospective cohort studies (8)										
Berkey, 2005[39]		X		X	XX		X	X	6	High
Bigornia, 2014[567]	X	X		X	X	X	X		6	High
DeBoer, 2015[561]	X	X		X		X		X	5	High
Dubois, 2016[580]	X	X	X	X			X		5	High
Huh, 2010[7]	X	X		X	XX	X		X	**7**	Low
Noel, 2011[8]	X	X		X	X	X	X		6	High
Scharf, 2013[563]	X	X		X	X	X	X		6	High
Wosje, 2001[565]	X	X		X		X		X	5	High
Total low risk										**1**

Notes:

- Each study can be awarded a maximum of one X for each numbered item within the Selection and Exposure categories.
- A maximum of two X's can be given for Comparability. Two stars were awarded if studies accounted for volume of milk consumed, prior weight status (birth weight for cross-sectional studies), and parent BMI. One star was awarded for adjusting for at least 4 other covariates. By design, cross-sectional studies were considered unable to achieve comparable cohorts; a maximum of 1 star could only be awarded.
- The original NOS uses stars, which were replaced with X's for ease of visual interpretation.
- We specified follow up time to be adequate if study duration exceeded 1 year.
- If missing/lost to follow up participants were not reported, no star was allocated.
- As per NOS guidelines, studies were considered low risk of bias if they received at least 7 stars[554].

Figure 1. Systematic Review Study Selection Process

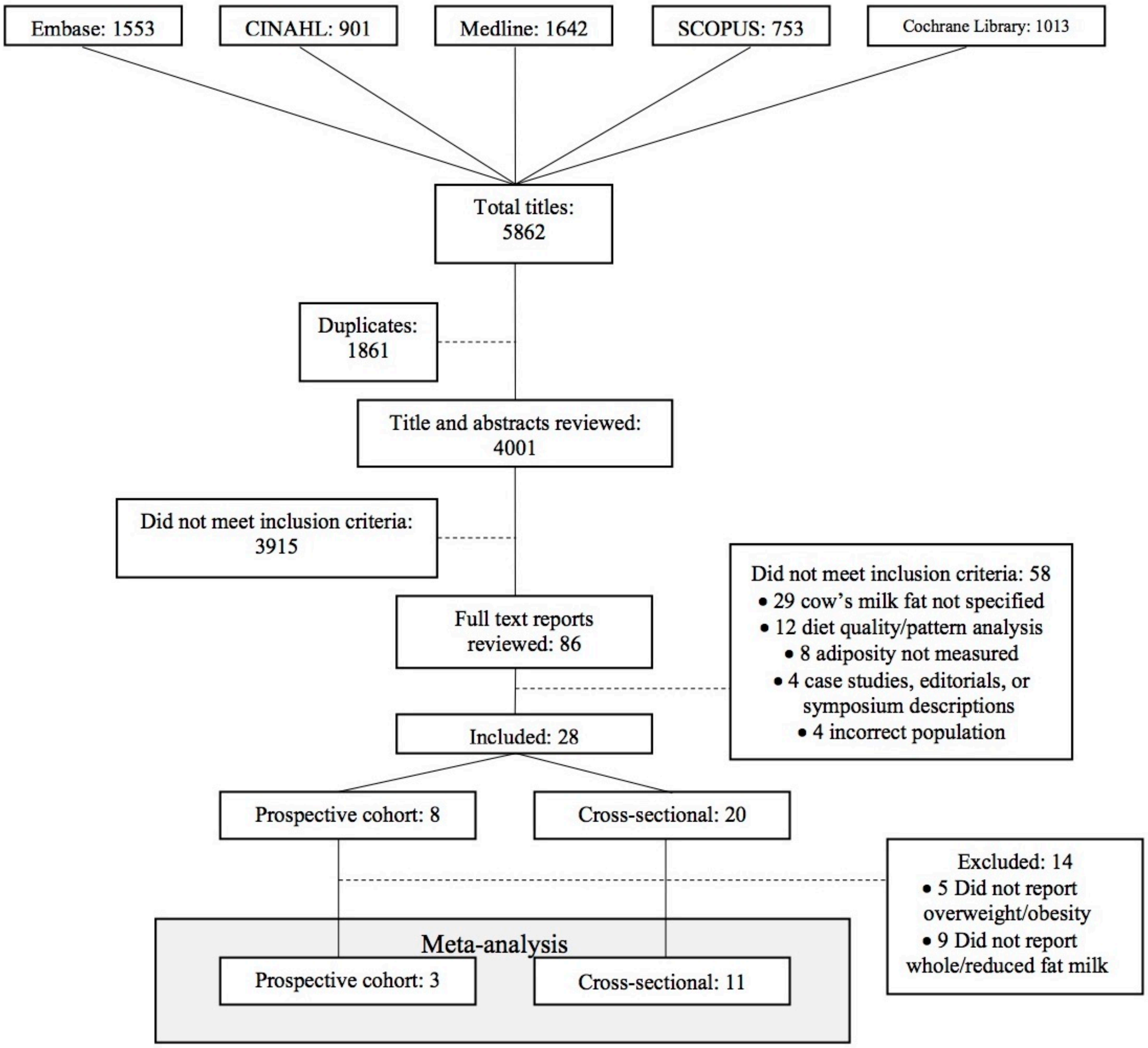
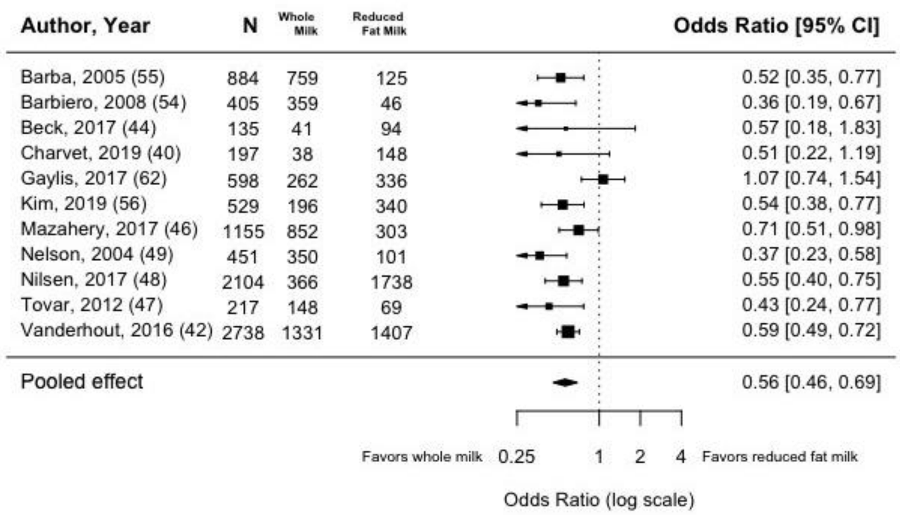
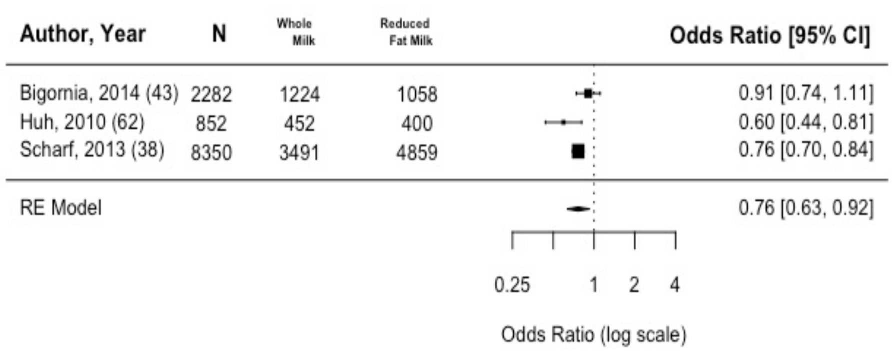


Figure 2. Crude odds ratio of overweight/obesity comparing children consuming whole milk vs. reduced fat milk.

Panel A: Cross-sectional studies only.

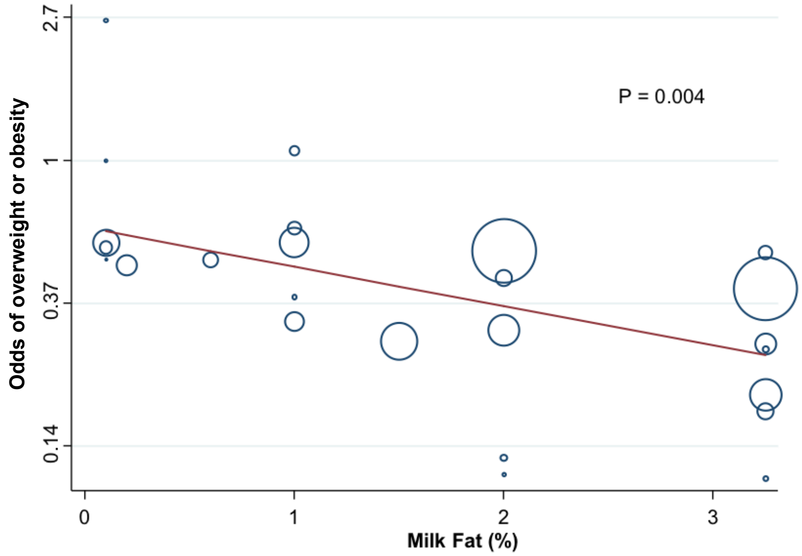


Panel B: Prospective cohort studies only.



Pooled effects were determined using random effects models. $I^2 = 73.8\%$. P values for pooled odds ratios: cross-sectional studies $p<0.0001$; prospective cohort studies $p= 0.006$.

Figure 3. Dose-response relationship between cow's milk fat and odds of overweight or obesity.



Seven studies provided data on 14,582 and were included in this analysis. Each circle represents a group of participants in each study consuming different cow's milk fat. The size of the circles represent the inverse of the variance of the group-specific log odds. P-value derived from a dose-response meta-regression with an odds ratio of 0.75 (95% confidence interval 0.65, 0.87, τ^2 = 0.010, I^2 = 64%).

CHAPTER 4: A QUALITATIVE STUDY TO UNDERSTAND PARENT AND PHYSICIAN PERSPECTIVES ABOUT COW'S MILK FAT FOR CHILDREN

4.1 ABSTRACT

Objectives: Consensus guidelines recommend that children consume reduced (0.1-2%) fat cow's milk at age 2 years to reduce the risk of obesity. Behaviours and perspectives of parents and physicians about cow's milk fat for children are unknown. Objectives were to 1) understand what cow's milk fat recommendations physicians provide to 2 year old children; 2) assess the acceptability of reduced fat vs. whole cow's milk in children's diets by parents and physicians; and, 3) explore attitudes and perceptions about cow's milk fat for children.

Design: Online questionnaires and individual interviews were conducted. Questionnaire data were analyzed using descriptive statistics. Interview transcripts were analyzed using a general inductive approach and thematic analysis.

Setting: The *TARGet Kids!* practice-based research network in Toronto, Canada.

Participants: Questionnaires included 50 parents and 15 physicians; individual interviews: 14 parents and 12 physicians.

Results: Physicians provided various milk fat recommendations for 2 year old children. Parents also provided different cow's milks: 18 (38%) provided whole milk and 29 (62%) provided reduced fat milk. Analysis of qualitative interviews revealed three themes: 1) healthy eating behaviours, 2) trustworthy nutrition information, and 3) importance of dietary fat for children.

Conclusion: Parents provide, and physicians recommend a variety of cow's milks for children, and hold mixed interpretations of the role of cow's milk fat in children's diets. Clarity about its effect on child adiposity is needed to help make informed decisions about cow's milk fat for children.

4.2 BACKGROUND

Parental choices about children's nutrition can be complex and involve a multitude of dynamic factors.[588] Parents utilize a range of resources (internet, family, friends, books) to provide knowledge and inform food choices[589] but they often seek physician guidance to provide unbiased information about healthy choices for their children.[590] For over a century, professional guidelines have recommended that parents provide cow's milk for children.[48,591] Cow's milk is a source of carbohydrates, fat, protein, vitamins and minerals, all of which are important for supporting child growth and development. For many children, cow's milk is a dietary staple and helps the transition from liquid to solid diets.[58,592]

Since 1992, the National Health Service[593] and Canadian Pediatric Society[51] has recommended that children switch from whole fat (3.25%) to reduced fat cow's milk (1%) at age 2 years to limit dietary fat intake and minimize risk of childhood obesity. This guideline was based on expert opinion and supported by a low GRADE level of evidence.[15,594] Two studies provided the scientific basis for this guideline. One was a randomized controlled trial that compared dietary counseling for increased unsaturated fat and decreased saturated fat and cholesterol intake (to a total of 30-35% energy from fat) to a free diet in Finland, and included 848 children aged 7-36 months.[274] The other was a 3-year longitudinal analysis of 8-10 year old children (N= 663) who participated in a randomized controlled trial in the United States, which compared dietary counseling for reduction of dietary fat (28% energy) to standard of care.[274] Results from these studies supported that consuming a fat-reduced diet during childhood was safe but provided little evidence to support a reduction in childhood obesity risk. Recent research has cast doubt on whether switching from whole to reduced fat milk at age 2 years is achieving its stated aim of reducing childhood obesity.[4,9,10,15,563,566,571]

The perspectives of parents and physicians about cow's milk fat for children are unknown as are the factors which contribute to parent and physician decision making about milk fat. Given that cow's milk is consumed by the majority of British and North American children,[58,67] understanding how parents and physicians make decisions about which fat content of cow's milk to provide to children is important in informing future research, practice guidelines and public nutrition policy.

The study objectives were to: 1) understand what fat content of cow's milk parents provide to children and what recommendations primary care physicians provide to parents; 2) assess the acceptability of physician recommendations for reduced fat vs. whole milk by parents and physicians; and, 3) explore parents' and physicians' attitudes and perceptions about cow's milk fat.

4.3 METHODS

Study Design

A mixed-methods study was conducted. A questionnaire was first used to understand current practices and perceptions about cow's milk fat among parents and physicians. Then, individual interviews were conducted through a purposive sample of parents and physicians to understand decision making and attitudes and perceptions around cow's milk fat.

Participants

All parents and physicians were recruited through the *TARGet Kids!* (The Applied Research Group for Kids) practice-based research network,[595] which is a collaboration of researchers and clinicians at the University of Toronto, St. Michael's Hospital, The Hospital for Sick Children, and McGill University. Interviews took place at two *TARGet Kids!* practice sites in Toronto.

Quantitative component

The purpose of the online questionnaire was to generate preliminary data to inform the qualitative interview guide, enabling further exploration of preliminary data. Participants were contacted by *TARGet Kids!* via email and invited to participate in an online questionnaire. A convenience sample of 15 parents (with 2-5 year old children) and 15 primary care pediatricians or family physicians were sought using Survey Monkey (surveymonkey.com).[596] The identity of respondents was not captured for confidentiality reasons. Information about what fat content of cow's milk parents provided to children older than 2 years of age and what milk fat recommendations physicians provided to parents was collected, in addition to parent and physician perceptions about milk fat (*see Supplementary Material: Questionnaire*). Responses to each question were quantified and descriptive statistics performed including means and proportions.

Qualitative component

The purpose of the individual interviews was to understand the rationale and attitudes behind questionnaire responses. This included exploring the elements that were meaningful for parents and physicians when providing or recommending different fat contents of cow's milk, parent and physician interactions during these encounters, and parent and physician attitudes towards cow's milk fat. A semi-structured interview guide was developed by an experienced qualitative researcher (CJP) to improve the validity of data collection (*see Supplementary Material: Interview Script*), and allowed the interviewer flexibility to pursue follow-up questions based on participant responses. The analysis of the transcripts occurred concomitantly with data collection according to the cyclic process of qualitative inquiry. Recruitment occurred through an iterative process until data saturation was reached, involving a minimum of 12 parents of children aged 2-5 years who drink milk and 12 physicians.[596] Interviews were 5 to 20 minutes in length and were conducted using an iterative approach. A convenience sample of parents were recruited in the waiting room of *TARGet Kids!*-affiliated pediatric and family practices, and physicians were recruited in their practice offices. The researcher conducting the interviews (SV) was a female PhD student with prior training in conducting interviews, and did not have pre-existing relationships with interviewees. Participants provided their age range (under 29, 30-39, or over 40 years), the number of children they had, and their children's ages.

Interviews were transcribed and de-identified (names and identifiable information removed). Participants did not review study transcripts or analysis results. Textual data were analyzed by one researcher (SV). Thematic analysis and general inductive approach were used to analyze and interpret the data. Text was coded and organized in categories, and themes were identified across the interviews guided by the research questions.[597] The researcher first familiarized herself with the data by reading and transcribing the interview transcripts. Then the data were coded, creating categories, building a coding scheme, identifying initial themes, reviewing and refining themes, and finally, naming and describing themes, including orienting each theme within the study context. Constant comparison analysis was conducted to analyze responses from parents and physicians in the main identified themes. Themes relevant to the research questions and objectives were identified and interpreted to understand core messages from both parents and physicians. After the themes were identified and described, physician and parent experiences and views were reviewed by the study team. Quotes that articulated repeated or recurring messages were chosen for inclusion in the study manuscript. Triangulation of researchers was employed (CJP and SV) to evaluate and improve reliability of the interpretation of results. NVivo 11 software was used for data organization and analysis.[598]

4.4 RESULTS

Quantitative component:

Online questionnaires were completed by 50 parents and 15 physicians. Milk fat recommendations were routinely provided by 9 of the 15 physicians (60%) at the 2 year well-child visit. Of these, 4 physicians recommended 2% milk (27%) and 5 physicians recommended whole milk (33%). Five physicians provided no milk fat recommendations (33%) and one physician did not provide an answer. Twenty-four of the 50 parents (48%) reported providing 2% milk to their children regularly, while 18 parents (36%) provided whole (3.25% fat) milk, 3 parents (7%) gave 1% milk, and 2 parents (4%) skim (0.1% fat) milk. Reasons for milk fat choice among parents included physician recommendation by 32 parents (64%), guideline recommendation by 19 parents (38%), and friend/family recommendation by 10 parents (20%). A few parents provided other reasons including "personal preference," "we buy one milk for the whole family," "my child needs extra fat," and "my child does not need extra fat."

Many parents and physicians believed that whole milk provided benefits to children over 2 years of age, which included healthier growth (36% of parents, 33% of physicians), brain development (30% of parents, 33% of physicians), and better nutrition (40% of parents, 33% of physicians). However, 38% of parents and 40% of physicians believed that whole milk did not provide any benefit, and 26% of parents and 60% of physicians believed that reduced fat milk did not provide any benefit. Forty-two percent of parents reported that reduced fat milk helped to reduce childhood obesity while few (13%) physicians held this view. All questionnaire results are shown in Table 9.

Qualitative component:

Individual interviews were conducted with 14 parents and 12 physicians. Most (n= 9) parents were 30-39 years old, while one parent was less than 29 years old and 4 were over 40 years old. Ten parents had two children, and four parents had one child. The mean age of parents' children was 3.6 (SD 1.2) years. All parents who were approached to participate did so. Three approached physicians refused to participate stating that they did not have time. Through the thematic analysis, three main themes were identified as being integral to views about cow's milk fat among parents and physicians: 1) healthy eating behaviours, 2) trustworthy nutrition information, and 3) importance of dietary fat for children. These themes were chosen based on their frequency in discussion with both parents and physicians, relevance to the context and objectives of the study, and emphasis observed by the researcher when interviewing participants.

Theme 1: Healthy eating behaviours

This theme was defined by the meaning of healthy food, who it is provided by and what it means to eat, provide, or recommend healthy food. Parents and physicians wanted children to develop healthy dietary habits from an early age. The term "healthy" was constructed differently by participants according to different information from trusted sources. Interview participants described healthy food as natural, unprocessed, containing vitamins and minerals, and recommended by a trusted source. A healthy diet was described as having a variety or a balance of foods in moderation, with appropriate amounts of carbohydrates, fat and protein. A healthy diet included the four food groups, and contained food for healthy growth and development. Foods containing "healthy fat" were considered healthy, but foods very high in fat or sugar were considered unhealthy. Some parents and physicians recognized that "low fat" foods can be higher in sugar.

Some parents and physicians described their habits or behaviours as "healthy," such as knowledge of healthy diets, providing or recommending nutritious foods for children, and encouraging healthy eating habits at home. Many parents mentioned limiting "unhealthy" foods such as red meat or sugar, but placed importance on foods viewed as "healthy" for children, such as "healthy fats," nuts, fruits and vegetables. It was evident that parents identified with their parenthood, but also in providing healthy food for their children.

> *"First off, [fat is important because] we want to make sure they grow up healthy and strong, so that's one. And also I believe you should foster a healthy eating habit early on, and it also has to do with body image, and identity."* – Parent

> *"I feel like whatever we give him is pretty healthy anyway, as long as it's balanced*."
>
> – Parent

Physicians were aware that their recommendations and interactions with parents and children were meaningful and had tangible effects. To be a "healthy" physician was to be reliable, reasonable, and flexible – to adapt to patients' needs and concerns while providing authoritative advice about behaviors and foods that would positively influence the health of their patients.

"My job is to keep them healthy." – Physician

Theme 2: Trustworthy nutrition information

This theme was defined by the trusted resources parents and physicians rely on to make decisions that affect the health of their children or patients. The leading trusted source of information among parents was physician guidance, and among physicians was clinical guidelines based on high-quality scientific evidence presented in peer-reviewed journal articles and clinical practice guidelines from reputable organizations (such as the Canadian Pediatric Society). Participants explained that their decisions about cow's milk fat were based on information they trusted.

Among physicians, trust in guidelines based on high quality scientific evidence was an important factor in providing nutritional recommendations to patients. Physicians trusted guidelines to be based on robust evidence, defined as research published in well-respected medical journals, from relevant populations, and using rigorous scientific methods. While physicians incorporated other relevant information (child weight and perceived risk of overweight or obesity, family socioeconomic status, other dietary factors such as volume of milk consumed) into their decision-making process, convincing scientific evidence was influential in decision making. Physicians were skeptical about research or publications with industry influence.

"Yes [I would like to be shown the evidence]. People will ask why…There needs to be some reason for having the full fat. A benefit, rather than safe. There needs to be a benefit." – Physician

I would have no problem recommending whole milk beyond 2 years of age if that was supported by the evidence. – Physician

Some physicians felt that the current guideline to transition from whole to reduced fat milk at age 2 years was reasonable while others questioned its utility and evidence base.

I think [the current guideline] makes it easy to give advice. But I question whether it's actually factual. -- Physician

[The current guideline] sounds reasonable to me, but I wonder with some patients whether that is the right thing to do- I don't know when to break that rule. – Physician

Physicians who questioned the guideline tended not to make any cow's milk fat recommendation, allowing parents to decide if and when to reduce milk fat content for their children. When asked if physicians would recommend whole milk beyond age 2 years, eleven of twelve interviewed physicians were willing to do so provided they were able to access, understand and communicate trusted evidence that whole milk was better for children than reduced fat milk. One physician expressed discomfort in recommending whole milk after age 2 years, as the physician was cautious about recommending too much dietary fat.

All physicians felt strongly that parents should know the volume of milk guideline (500 mL, or 2 servings per day), regardless of fat content of milk provided. Several voiced concerns about children consuming a large quantity of milk daily.

I think it's a low-hanging fruit to come down on the cow's milk [fat], because they're already drinking a lot of it, it's an easy way to reduce calories in the diet. – Physician

Parents viewed their children's physician as the most trustworthy source of information when making decisions concerning the health of their children. Although parents received information from peers, the internet, and books, they were aware that this was subject to inaccuracy and inapplicability to their own children. Physicians established trusting relationships with parents by demonstrating knowledge, critical thinking, and skilled expertise in their practice, ultimately providing the best possible care and recommendations unique to each child. Parents frequently said that their child's physician had the best interest of their child in mind, used current, robust research to make recommendations appropriate for their child, and would provide recommendations specific to their child's individual needs. Physicians were described as knowledgeable, well-educated, trustworthy, and held in high esteem.

> *"If someone told me to do something in the best interest of my daughter, definitely I'd investigate further, but I wholeheartedly trust the pediatrician. I have not gone to medical school, I don't have the expertise. So that's a trusted source for me. If he's saying something, it's probably sound."* – Parent

> *"[Physicians who make recommendations] have research to support it."* - Parent

When asked about providing whole milk to children older than age 2 years, 12 of 14 parents were willing to do so at the recommendation of their children's physician. Some parents would require further explanation, rationale, or support from the physician; others would accept a physician recommendation without additional details. Two parents stated that they would not feel comfortable providing whole milk beyond age 2 years because of concerns about excess dietary fat.

Theme 3: Importance of dietary fat for children

This theme was defined by the perception of dietary fat in children's diets, and what it means to provide fat to children. Parents and physicians were aware that children need a higher proportion of dietary fat than adults because of its role in growth and development. They recognized the importance of fat for brain development, physical activity levels in children, and overall growth. However, *too much* dietary fat was concerning for both parents and physicians, as they believed excess dietary fat would lead to excess adipose tissue. Parents and physicians were concerned about too much fat in children's diets, and were cautious not to provide too much fat to reduce their children's risk of overweight or obesity. Too much fat was viewed with negative implications but not well defined. Parents and physicians placed importance on preventing childhood overweight and obesity. They sought simple, actionable and effective ways to reduce the risk of obesity early in life, including dietary strategies.

> *"I think fat is good, as long as you don't have too much."* – Parent

> *"He needs it to grow- he's growing lots of cells, he needs fat, so I don't have a problem with giving him fat, I just don't want to give him too much."* – Parent

Despite concern about too much dietary fat among parents and physicians, parents repeatedly referred to cow's milk fat as "healthy," "essential," "unprocessed" and "natural." Parents viewed cow's milk as an appropriate food for their children, including the fat it provides. This perspective allowed parents to feel comfortable providing it to their children, and seemed to bring parents a sense of assuredness that their children were receiving proper nutrition.

> *"I do believe milk is a source of healthy fat so I wouldn't really question it, and I actually do think it's probably healthy, nutritious for kids."* – Parent

Physicians acknowledged cow's milk as a suitable food for children, especially young children transitioning from fluid to solid diets. However, physicians commented on the proportion of children who are served too much milk, due in part to convenience, likability on behalf of children, and parents' positive views of milk. Physicians felt that some parents perceived milk as such a nutritious food, they seemed not to limit their child's consumption, leading children to consume excess calories and fat.

> *"You just give a couple cups of milk a day and that helps to give the essential fat."*
>
> -- Physician

Physicians also wondered about the appropriate amount of fat for children, including effects on future well-being.

> *"I wonder about the impact longitudinally on cardiac health or diabetes. What have [the current milk fat] guidelines done on the long term effects?"* – Physician

4.5 DISCUSSION

In this mixed-methods study, questionnaires and individual semi-structured interviews were used to understand how parents and physicians make milk fat recommendations for children. Parents and physicians were similarly divided about providing or recommending whole milk, reduced fat milk, or no milk fat for children 2 years of age or older. Through a thematic analysis of parent and physician interview transcripts, three themes were identified: 1) healthy eating behaviours, 2) trustworthy nutrition information, and 3) importance of dietary fat for children. These themes were helpful in understanding how parents and physicians use trusted resources to develop healthy habits and behaviours which informed perceptions about foods viewed as best for children's nutrition and development.

Within the "healthy food" theme, an identity phenomenon emerged among both parents and physicians. Parents and physicians who identified as being "healthy" felt it important to act according to their beliefs, identity, and knowledge by providing or recommending what they determined to be "healthy" for children. Beyond objective classification of foods based on nutritional content, parents classified foods as being healthy based on their preferences, beliefs, or identity. It has been described that an individual's determination of a "healthy food" is highly variable and dependent on beliefs,[599] experiences,[600] perceptions[601] and likes or dislikes.[602] Results of this study suggest that if parents believe they are providing a healthy diet to children, many foods can be described as healthy because the parent had chosen to provide it, or a trusted resource described it as such. For example, some parents felt justified in providing whole milk to children because extra fat was needed for growth, while parents who provided reduced fat milk believed that providing less fat was needed. Moderation and balance about fat consumption were frequently mentioned by both parents and physicians, which is consistent with other studies that asked participants to define "healthy diets."[601,603] As Lupton and Chapman point out, "by using the concept of moderation, people could justify any food choice."[604]

The themes of trust and healthy food intersected where some parents regarded physician opinion and guidance as superior to other information sources. Similarly, physician trust in guidelines that were perceived to be based on high-quality evidence helped maintain their duty to keep children healthy. However, parents who had more knowledge or experience in nutrition and physicians who were more versed in current literature deviated from guideline-based recommendations. This knowledge and experience may have resulted in heightened confidence and autonomy. Further, well-established "healthy" identities may have allowed for personal judgment to override commonly-held beliefs. Knowledge about nutrition has been shown to be a determinant of dietary behavior, where interest and importance placed on nutrition often varies with nutrition knowledge.[605] Less educated or less experienced parents or physicians may have felt more reliant on experts and not as free to deviate from guidelines or advice. This has been noted in other literature. Hart et al. described that individuals of higher socioeconomic status or higher educational attainment had less reliance on nutrition guidelines and more reliance on an innate knowledge about food.[606] According to Bisogni et al., a person's diet is a manifestation of a variety of factors, such as knowledge, attitudes towards food and socioeconomic status.[588]

An overwhelming number of parents identified cow's milk fat as "natural," "unprocessed," and "healthy." This finding was remarkable because the term "healthy fat" is commonly associated with unsaturated fat, whereas "unhealthy fat" is another term for saturated fat, which are most of the fatty acids in cow's milk. This discrepancy may have occurred because parents are told by trusted sources that cow's milk is healthy for children; therefore, cow's milk fat must be the "healthy" variety. However, many parents voiced that they tried not to provide their child "too much fat." While no amount of fat was defined as "too much," parents and physicians recognized that a high proportion of dietary fat would likely cause weight gain. This ambiguity may have contributed to the varied recommendations physicians reported providing at 2-year well-child visits, and differing fat contents of cow's milk parents served to children over age 2 years. Though some opinions held by participants were strong (cow's milk is healthy, children need dietary fat), ambiguity in terms such as "healthy food," "too much fat," and "healthy fat" may have caused parents difficulty in discerning how much dietary fat to provide their children. Parents tended to rely on physicians, who used guidelines based on research to direct their practice. The strength of evidence on which these guidelines are based was acknowledged by only a few physicians, who also tended not to provide cow's milk fat recommendations. Overall, the varied regular practice of parents and physicians indicated by the quantitative component of this study reflects the uncertainty of evidence, varied confidence in current guidelines, and mixed messages parents receive as a result.

This study has a number of strengths. Recruitment took place in a primary care setting, which allowed us to obtain a sample of participants highly relevant to our research questions. Semi-structured interviews were informed by a quantitative questionnaire which provided focus and facilitated the identification of perspectives and ideas which may not easily be captured by other research methods. The semi-structured interviews allowed the interviewer to respond flexibly to participant responses, obtaining further details when appropriate, contributing to data richness. Data saturation was also considered to be reached by the interviewer, indicating a wide variety of viewpoints had been richly captured. Thematic analysis provided understanding of participant views and ideas which were directly related to our research questions and overarching concepts.

This study also had a number of limitations. Interviewer views and perspectives are implicit in qualitative methods involving interviews. The interviewer was aware of some biases she may have introduced to participant discussion, such as knowledge of clinical nutrition guidelines, and current literature on the topic of children's nutrition. However, interview questions were reviewed by other researchers (JM, CJP) to mitigate risk of a biased script, and a reflexive journal was kept by the analyst during the whole analysis, interpretation, and writing stages to minimize the projection of their individual views and thoughts. Online questionnaires did not capture the social identity of participants, or their views and behaviors related to their social role, which may have allowed persons other than participating *TARGet Kids!* physicians or parents to complete them. Although all parents who were approached to participate did so, participant views may be different than those of individuals who declined to participate in research activities, received or provide healthcare outside of the *TARGet Kids!* practice based research network or did not have access to primary healthcare. Responses obtained by this study may also not be generalizable to other populations. However, data saturation was considered to be reached in the interviews, suggesting that many ideas were shared among participants in this study, which may be generalizable to populations outside of this study sample.

4.6 SIGNIFICANCE

Most parents and physicians strive for their children and patients to be healthy. Parents trust physicians to make recommendations in their best interest, and physicians trust high-quality evidence. But, lack of clarity about the effect of cow's milk fat on childhood weight status resulted in ambiguity about what amount of cow's milk fat is perceived as "healthy" for both parents and physicians. A better understanding of the effect of cow's milk fat on childhood adiposity would help parents and physicians make informed decisions. Understanding how parents and physicians place trust in information sources, use existing knowledge, and use their identity to shape decisions may be helpful for future research and policy recommendations about milk fat for children.

Table 9. Questionnaire responses about cow's milk fat of parents of children aged 2-5 years who drink cow's milk (n=50) and physicians (n=15) participating in the TARGet Kids! research network.

Question	Parents, n (%)	Physicians, n (%)
What cow's milk fat recommendation do you typically make during the 2-year well-child visit?		
Skim		0 (0)
1%		0 (0)
2%		4 (27)
Whole		5 (33)
None		5 (33)
What cow's milk fat recommendation did your child's physician make during their 2-year well-child visit, if any?		
Skim	0 (0)	
1%	1 (2)	
2%	18 (36)	
Whole	11 (22)	
None	11 (22)	
Don't know	8 (16)	
What fat content of cow's milk do you usually provide to your child?		
Skim	2 (4)	
1%	3 (6)	
2%	24 (48)	
Whole	18 (36)	
Why do you choose this fat content of cow's milk for your child?		
Recommended by physician	19 (38)	
Recommended by guideline	11 (22)	
Recommended by friend/family	6 (12)	
Other	17 (34)	
What dietary recommendations do you usually provide to parents of ~2 year old children whom you or the parent suspects is at risk of overweight/obesity?		
Reduce sugar-sweetened beverages		13 (87)
Reduce bottle use		14 (93)
Reduce fat intake		1 (7)
Reduce % fat of milk		3 (20)
Increase % fat of milk		1 (7)
Reduce kcal intake		2 (13)
Increase fruit/veg		14 (93)
Structure meals/snacks		12 (80)
What dietary recommendations do you usually provide to parents of ~2 year old children whom you or the parent suspects is at risk of underweight?		
Increase kcal intake		12 (80)

Reduce % fat of milk		0
Increase % fat of milk		8 (53)
Increase meals/snacks		4 (9)
Food fortification		3 (20)
What do you think is the ideal fat content of cow's milk for children over age 2 years?		
Skim		0 (0)
1%		1 (7)
2%		7 (47)
Whole		7 (47)
What do you think are the benefits of providing children older than 2 years of age with whole (3.25% fat) milk (select all that apply)?		
Better body composition	6 (12)	2 (13)
Healthier growth	18 (36)	5 (33)
Brain development	15 (30)	5 (33)
Obesity prevention	5 (10)	2 (13)
Better nutrition	20 (40)	5 (33)
None	19 (38)	6 (40)
What do you think are the harms of providing children older than 2 years of age with whole (3.25% fat) milk (select all that apply)?		
May cause weight gain	19 (38)	5 (33)
Higher fat intake	21 (42)	4 (9)
None	17 (34)	10 (67)
What do you think are the benefits of providing children older than 2 years of age with reduced fat (1 or 2% fat) milk (select all that apply)?		
Better body composition	12 (24)	2 (13)
Healthier growth	11 (22)	1 (7)
Brain development	1 (2)	1 (7)
Obesity prevention	21 (42)	2 (13)
Better nutrition	7 (14)	1 (7)
None	13 (26)	9 (60)
What do you think are the harms of providing children older than 2 years of age with reduced fat (1 or 2% fat) milk (select all that apply)?		
May cause weight gain	4 (8)	1 (7)
May cause weight loss	6 (12)	0 (0)
Lower fat intake	29 (58)	3 (20)
None	12 (24)	11 (73)

CHAPTER 5: COW'S MILK FAT AND CHILD ADIPOSITY: A PROSPECTIVE COHORT STUDY

5.1 ABSTRACT

Background. International guidelines recommend children aged 9 months to 2 years consume whole (3.25%) fat cow's milk, and children older than age 2 years consume reduced (0.1-2%) fat cow's milk to prevent obesity. The objective of this study was to evaluate the longitudinal relationship between cow's milk fat (0.1-3.25%) intake and Body Mass Index z-score (zBMI) in childhood.

Methods. A prospective cohort study of children aged 9 months to 8 years was conducted through the TARGet Kids! primary care research network. The primary exposure was cow's milk fat consumption (skim (0.1%), 1%, 2%, whole (3.25%)), assessed by parental report. The primary outcome was zBMI. Height and weight were measured by trained research assistants and zBMI was determined according to WHO growth standards. A linear mixed effects model and logistic generalized estimating equations were used to determine the longitudinal association between cow's milk fat intake and child zBMI.

Results. Among children aged 9 months to 8 years (N= 7467), each 1% increase in cow's milk fat consumed was associated with a 0.05 lower zBMI score (95% CI -0.07 to -0.03, $p < 0.0001$). Compared to children who consumed reduced fat (0.1-2%) milk, there was evidence that children who consumed whole milk had 16% lower odds of overweight (OR= 0.84, 95% CI 0.77 to 0.91, $p < 0.0001$) and 18% lower odds of obesity (OR= 0.82, 95% CI 0.68 to 1.00, $p = 0.047$).

Conclusion. Guidelines for reduced fat instead of whole cow's milk during childhood may not be effective in preventing overweight or obesity.

5.2 INTRODUCTION

One in three children in North America are living with overweight or obesity.[607] Childhood obesity has been associated with lower self-esteem[608] and higher risk of mood disorders.[609] Childhood obesity also tracks into adulthood,[610] increasing the risk of cardiovascular disease over the life course.[611]

Cow's milk is widely consumed in childhood[58,66] and contains nutrients which support growth and development, such as protein, fat, calcium, phosphorous and vitamin D. The American Academy of Pediatrics and American Heart Association,[612] the Canadian Pediatric Society,[304] and National Health Service (UK)[54] recommend that children consume whole (3.25% milk fat) cow's milk until 2 years of age and then switch to reduced (0.1-2% milk fat) cow's milk to lower the risk of overweight or obesity. A recent systematic review and meta-analysis of observational studies revealed evidence that whole milk was associated with lower risk of child overweight or obesity among children aged 9 months to 18 years.[613] These findings were largely based on low quality cross sectional studies which did not adjust for potential confounding factors such as volume of milk consumed or previous child weight or social determinants of health. The current study was designed to overcome these weaknesses and minimize risk of bias through a large prospective cohort study with adjustment for important potentially confounding factors. We hypothesized that children who consumed higher cow's milk fat would have lower adiposity and be less likely to have overweight or obesity compared to children who consumed lower cow's milk fat.

The primary objective of this study was to evaluate the relationship between cow's milk fat consumption and child adiposity, assessed using Body Mass Index z-score (zBMI) among healthy children aged 9 months to 8 years. The secondary objective was to determine the relationship between whole vs. reduced fat (0.1-2%) cow's milk consumption and odds of overweight and obesity.

5.3 METHODS

Participants and setting

A prospective cohort study was conducted through the TARGet Kids! (The Applied Research Group for Kids) primary care research network in Toronto, Ontario, Canada. Children were followed through TARGet Kids! between August 2008 and April 2019 during regularly scheduled well-child visits at twelve pediatric and family practices.[595] Healthy children aged 9 months to 8 years who reported consuming cow's milk were included. Exclusion criteria were children with severe developmental delay, birth weight <2500 grams, chronic illness impacting metabolism (e.g. cystic fibrosis).

Exposure

The primary exposure was cow's milk fat consumption. This was measured through a parent-completed dietary questionnaire based on the Canadian Community Health Survey.[614] Parents were asked, "Please specify your child's diet for the past 3 days: skim (0.1%), 1%, 2%, homo (3.25%) milk." If parents indicated more than one milk fat, responses were averaged. The secondary analysis categorized the exposure as whole (3.25%) or reduced (0.1-2%) fat cow's milk consumption.

Outcome

The primary outcome was Body Mass Index z-score (zBMI), which is an age and sex adjusted measure of body weight. Trained research assistants measured child weight in kilograms and height in metres using a Healthometer digital baby scale and standardized recumbent length board (SECA, FL), respectively, for children younger than 2 years of age. Weight and height were measured using a Healthometer stadiometer (SECA, FL) for older children. Body Mass Index was calculated by dividing weight (kg) by height squared (m^2) and z-scores were determined according to the World Health Organization (WHO) growth standards. For secondary outcomes, categories for normal weight, overweight and obesity were: $-2 \leq$ zBMI ≤ 1 normal weight, $1 <$ zBMI ≤ 2 overweight, zBMI > 2 obesity, consistent with WHO recommended weight status categorization.[615] For the purpose of this manuscript and consistency across ages, we applied WHO weight classifications for children over age 5 years to all children in our sample.[616,617]

Covariates

Clinically relevant covariates which have been proposed in the literature to have a relationship with cow's milk fat or childhood adiposity were specified *a priori* through a detailed literature review. These included volume of cow's milk, volume of sugary drinks (including 100% juice, fruit drinks, and soft drinks) consumed in 250 mL cups per day, maternal ethnicity, self-reported family income, birth weight in kilograms, breastfeeding duration in months, and parent BMI. Dietary information, maternal ethnicity, family income, breastfeeding duration and birth weight were collected using the same questionnaire as used to measure cow's milk fat consumption. Volume of cow's milk and sugary drinks was measured with the question, "Circle how many cups of each drink your child has currently in a typical day: 0, ½, 1, 2, 3, 4, 5+." Trained research assistants measured parental height and weight using a Healthometer stadiometer (SECA, FL) and BMI was calculated as weight (kg) divided by height squared (m^2).

Statistical analysis

Descriptive statistics were used to characterize participants. To determine the longitudinal association between cow's milk fat consumption and child zBMI, a linear mixed effects model was used. Linear mixed effects models have the advantage that all repeated measures provided by each participant can be used and within-subject correlation can be accounted for using subject specific random intercepts. For the primary analysis, unadjusted and adjusted (see covariates above) models were created with cow's milk fat as the exposure and zBMI as the outcome. Restricted cubic splines for age with 5 knots were used to evaluate non-linear trajectories of the observed relationships in keeping with previous research in the same cohort.[618] For the secondary analysis, logistic generalized estimating equations (GEE) were used to examine the relationship between cow's milk fat and odds ratio (OR) of overweight excluding obesity ($1 < zBMI \leq 2$) and obesity ($zBMI > 2$) relative to normal weight ($-2 \leq zBMI \leq 1$).

All covariates had less than 15% missing data. Missing data was handled using multiple imputation using 18 imputed datasets using all covariates.[619] Sensitivity analyses were conducted among children with and without missing data to assess for consistency of results. For all statistical tests, an alpha level of 0.05 was used and 95% confidence intervals were calculated. Multicollinearity was measured using the variance inflation factor, which remained under 1.5 for all covariates.[620] All analyses were conducted using the geepack,[621] multgee,[622] nlme[623] and lme4[624] packages in R version 3.5.1.[625]

All parents of children participating in this study provided informed written consent, and ethics approval was obtained from the Hospital for Sick Children and Unity Health Toronto.

5.4 RESULTS

A total of 7467 children aged 9 months to 8 years were included in the analysis (Figure 4). Baseline characteristics of participating children are described in Table 10. At baseline, the mean child age was 2.6 (SD 1.5) years, and 53% of participants were male. The mean zBMI at baseline was 0.18 (SD 1.1); 77% of children had normal weight, 16% had overweight excluding obesity, 5% had obesity, and 2% had underweight. The majority (56%) of children consumed whole cow's milk at baseline, followed by 2% milk (34% of children), 1% milk (8% of children) and skim milk (3% of children). On average, children were reported to consume 1.9 (SD 1.2) 250-mL cups of cow's milk per day at baseline. The mean follow-up duration was 2.7 years (SD 1.7).

For the primary analysis, the unadjusted linear mixed model revealed that on average with every 1% increase in cow's milk fat consumed (for example, 2% vs. 1%, 1% vs. skim, etc.), children had 0.05 lower zBMI (95% CI -0.07 to -0.03, $p < 0.0001$). For example, a 4 year old child who consumed whole milk had on average 0.1 kg lower body weight than a 4 year old child with the same height consuming reduced fat milk. When adjusted for all pre-specified covariates, the relationship remained unchanged (Table 11). Figure 5 shows the adjusted longitudinal relationship between cow's milk fat, dichotomized into reduced (0.1-2%) fat and whole (3.25%) fat milk, and child zBMI.

In the secondary analysis, odds ratios for overweight and obesity among children who consumed whole vs. skim (0.1%), 1% and 2% cow's milk were estimated (Table 12 and Figure 6). When analyzed in a multinomial logistic GEE model, there was evidence that children who consumed whole cow's milk had 16% lower odds of overweight (OR= 0.84, 95% CI 0.77 to 0.91), $p < 0.0001$) and 18% lower odds of obesity (OR= 0.82, 95% CI 0.68 to 1.00, $p = 0.047$) compared to children who consumed reduced (0.1-2%) fat cow's milk.

5.5 DISCUSSION

In this prospective cohort study of 7467 healthy children aged 9 months to 8 years, higher cow's milk fat consumption was associated with lower child zBMI after controlling for potential confounding factors including volume of milk consumed, parent BMI, and birth weight. There was evidence that children who consumed whole milk had 16% lower odds of overweight and 18% lower odds of obesity relative to children who consumed reduced fat (0.1-2%) milk.

Professional recommendations from the American Academy of Pediatrics, Academy of Nutrition and Dietetics, American Heart Association,[612] Health Canada and the Canadian Pediatric Society[237] recommend that children consume whole cow's milk until age 2 years, and then transition to reduced (0.1-2%) fat cow's milk to reduce the risk of excess adiposity. These guidelines are based on consensus opinion[15] and evidence from the 1990's supporting that reduced fat cow's milk is safe for children to consume.[274,626] Our findings support the guideline for children aged 9 months to 2 years, but suggest that guidelines for older children may not be effective in preventing child overweight or obesity.

Findings from the present study are consistent with several other studies. A recent systematic review and meta-analysis identified 28 observational studies which examined the relationship between cow's milk fat and child adiposity among children aged 9 months to 18 years.[613] An association between higher cow's milk fat and lower adiposity was found in 18 studies, and 10 studies reported no evidence of a relationship. Among three longitudinal studies included in the meta-analysis, which involved 11,484 children aged 2-13 years, children who consumed whole cow's milk had 0.76 the odds of overweight or obesity (95% CI 0.63 to 0.92, p= 0.006) compared to children who consumed reduced fat (0.1 to 2%) cow's milk. However, 27 of the studies, including 7 of the 8 prospective cohort studies, were considered to have high risk of bias due to cross sectional design or lack of adjustment for potential confounding factors such as volume of milk, prior measures of adiposity, and parent BMI. The current study was designed to overcome these weaknesses through a large prospective cohort study with adjustment for important potentially confounding factors.

Possible mechanisms underlying the observed relationship include reverse causality, where parents of leaner children provide higher cow's milk fat and vice versa. One qualitative study sought to understand if mothers considered child adiposity when choosing cow's milk fat for their children and revealed that those who perceived their children to be overweight or obese tended to choose reduced fat milk instead of whole milk, but that mothers' perception of children's weight status was correct only 63% of the time.[82] Other studies have identified that parent perception of child adiposity tends to be underestimated.[627,628] Another possibility is that children who consume higher cow's milk fat are more satiated than those who consume reduced fat cow's milk, leading them to consume a lower quantity of cow's milk or other energy dense foods contributing to higher energy intake.[448] Hormones secreted in response to whole milk consumption such as cholecystokinin and glucagon-like peptide 1 may also play a role in this relationship.[21,441] Cow's milk fat contains unique fatty acids such as trans-palmitoleic acid and conjugated linoleic acid,[127] which may provide metabolic benefits relative to other fatty acids.[437] This theory suggests that cow's milk fat may not contribute to energy storage and adipose tissue as significantly as other types of dietary fat.[22,27] Future studies are needed to understand the mechanism underlying the relationship between cow milk fat and child adiposity, including randomized controlled trials to mitigate influence of confounding factors and establish temporality.

This study had several strengths. The large, diverse cohort of healthy children who were followed over many years provided rich information about nutrition through early and middle childhood. In addition, a number of clinically relevant covariates were controlled for which reduced the risk of confounding. Complex statistical modeling using random effects models minimized within-subject correlation and improved model estimate accuracy. Restricted cubic splines allowed for evaluation of non-linear trends over time. Repeated measures data allowed us to account for the directionality of this relationship, which improved upon the cross-sectional methods of previous studies by adding power and adjusting for within-subject measures.

This study had a number of weaknesses. Although cow's milk volume and sugary drink consumption were accounted for, there was insufficient data to calculate total daily energy which would have improved our understanding of the mechanism underlying the observed relationship. While zBMI is a measure preferred by clinicians because it is simple to interpret and track over time, it is not a direct measure of body composition which would improve measurement of child adiposity.[334] While participants in this study were from an ethnically diverse population of healthy of urban Canadian children, they may not be representative of other groups of children. Further, cow's milk with different fat contents may have been offered to children based on parent perception of body size. Data on reasons for milk fat choices would have helped to clarify whether reverse causality contributed to the observed results, but this was not available.

In this prospective cohort study of healthy children age 9 months to 8 years, higher cow's milk fat consumption was associated with lower zBMI and lower odds of overweight and obesity. Given that the majority of North American children consume cow's milk daily, this study raises the possibility that whole cow's milk may play a role in lowering the risk of childhood overweight or obesity. Randomized trial data showing the relationship between cow's milk fat and child adiposity is needed to confirm these findings.

Table 10. Participant characteristics (N= 7467) at baseline.

Child characteristics	
Age, years, mean (SD)	2.6 (1.5)
Gender, male, n (%)	3930 (53)
zBMI, mean (SD)	0.18 (1.1)
Thinness (zBMI < -2), n (%)	170 (2)
Normal weight (-2 ≤ zBMI ≤ 1), n (%)	5764 (77)
Overweight (excluding obesity; 1 < zBMI ≤ 2), n (%)	1173 (16)
Obesity (zBMI > 2), n (%)	355 (5)
Cow's milk consumed in the past 3 days*	
Skim (0.1%), n (%)	226 (3)
1%, n (%)	562 (8)
2%, n (%)	2501 (33)
Whole (3.25%), n (%)	4178 (56)
Reported typical cow's milk volume consumed, cups/day, mean (SD)	1.9 (1.2)
Parent BMI, mean (SD)	25.3 (4.9)
Maternal ethnicity, n (%)*	
European	4425 (59)
East Asian	458 (6)
South Asian	587 (8)
Southeast Asian	239 (3)
Arab or African	486 (7)
Latin American	208 (3)
Mixed ethnicity	383 (5)
Other	22 (0.3)
Self-reported household income ($), n (%)**	
<30,000	719 (10)
30,000-79,999	1222 (16)
80,000-150,000	3584 (48)
>150,000	251 (3)
Sugary drink intake, cups/day, mean (SD)	0.7 (1.1)
Serum 25-hydroxyvitamin D, nmol/L, mean (SD)	87.9 (29.4)
Birth weight, kg, mean (SD)	3.3 (0.6)
Breastfeeding duration, months, mean (SD)	10.7 (7.5)
Follow-up duration, years, mean (SD)***	2.7 (1.7)

*n=659 children with missing maternal ethnicity.
**n=1691 children with missing household income.
***Not a baseline characteristic.

Table 11. The relationship between cow's milk fat intake and child zBMI.

	Unadjusted		**Adjusted***	
	Coefficient (95% CI)	**p value**	**Coefficient (95% CI)**	**p value**
Cow's milk fat (%)	-0.05 (-0.07 to -0.03)	<0.0001	-0.05 (-0.07 to -0.03)	<0.0001

N=7467. *A linear mixed model was used and adjusted for volume of cow's milk, volume of sugary drink intake (including 100% juice, fruit drinks, and soft drinks) consumed in 250 mL cups per day, maternal ethnicity, self-reported family income, birth weight in kilograms, breastfeeding duration in months, and parent BMI. Covariate coefficient estimates not shown.

Table 12. The relationship between cow's milk fat intake and odds of overweight (excluding obesity) and obesity relative to normal weight (-2< zBMI ≤1), adjusted for clinically relevant covariates.*

	Overweight (1< zBMI ≤ 2)		**Obesity (zBMI >2)**	
	aOR (95% CI)	p value	aOR (95% CI)	p value
Whole vs. 0.1-2%	0.84 (0.77 to 0.91)	<0.0001	0.82 (0.68 to 1.00)	0.047
Whole vs. 2%	0.81 (0.74 to 0.89)	<0.0001	0.83 (0.68 to 1.00)	0.05
Whole vs. 1%	0.96 (0.82 to 1.11)	0.57	0.87 (0.66 to 1.16)	0.35
Whole vs. 0.1%	0.83 (0.66 to 1.03)	0.09	0.69 (0.45 to 1.05)	0.08

*N=7467. aOR= Adjusted Odds Ratio. Logistic generalized estimating equations were used and adjusted for volume of cow's milk, volume of reported sugary drink intake (including 100% juice, fruit drinks, and soft drinks) consumed in 250 mL cups per day, maternal ethnicity, self-reported family income, birth weight in kilograms, breastfeeding duration in months, and parent BMI. Covariate coefficient estimates not shown.

Figure 4. Participant flow diagram.

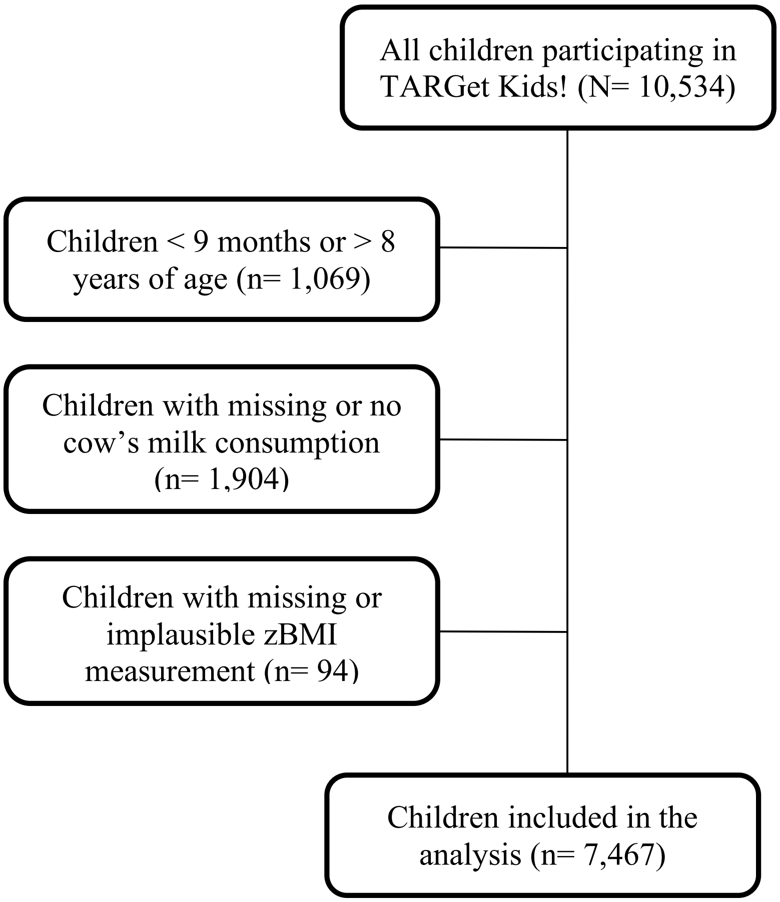
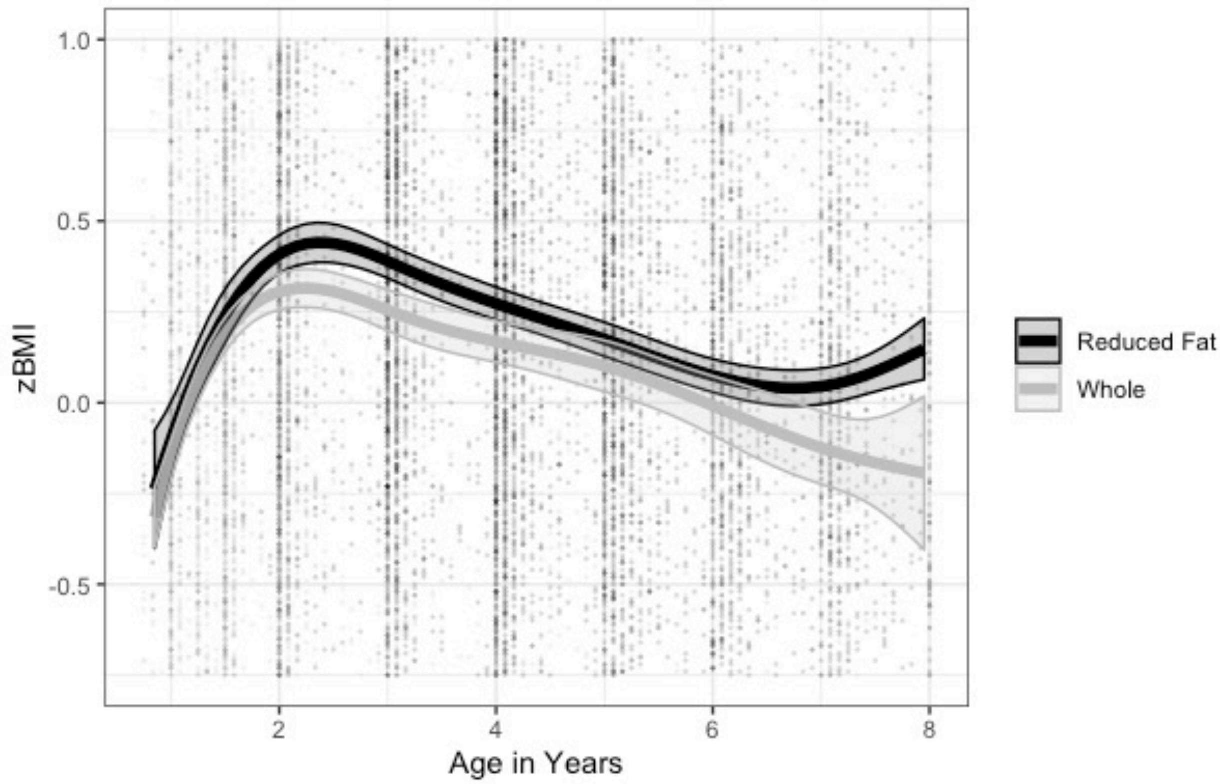
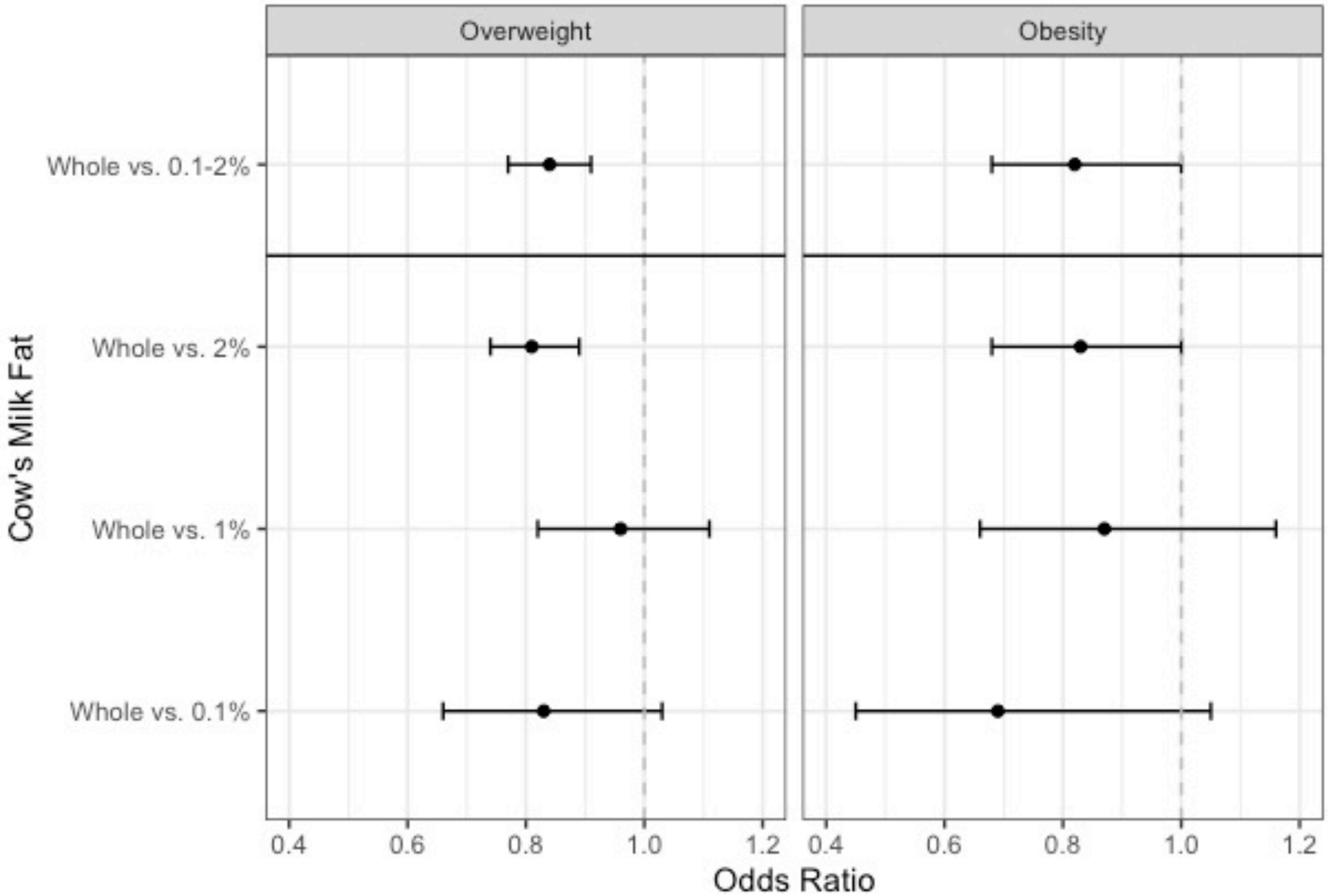


Figure 5. The relationship between cow's milk fat and zBMI in children aged 9 months – 8 years, adjusted for clinically relevant covariates.



Individual data points are represented by small circles in the background. Shades of circles correspond to cow's milk fat consumed by children according to the figure legend.

Figure 6. Odds of overweight (excluding obesity; $1 < zBMI \leq 2$) and obesity ($zBMI > 2$) among children who consumed different cow's milk fat, adjusted for clinically relevant covariates.



Error bars represent 95% confidence intervals.

CHAPTER 6: COW'S MILK FAT OBESITY PREVENTION TRIAL (COMFORT): A PRIMARY CARE EMBEDDED RANDOMIZED CONTROLLED TRIAL TO DETERMINE THE EFFECT OF COW'S MILK FAT ON CHILD ADIPOSITY

6.1 ABSTRACT

Introduction: Cow's milk is a dietary staple for children in North America. Though public health guidelines suggest children transition from whole (3.25% fat) milk to reduced (1% or 2%) fat milk at age 2 years, recent epidemiological evidence supports a link between whole milk consumption and lower adiposity in children. The purpose of this trial is to determine which milk fat recommendation minimizes excess adiposity and optimizes child nutrition and growth.

Methods and analysis: CoMFORT (Cow's Milk Fat Obesity pRevention Trial) will be a pragmatic, superiority, parallel group randomized controlled trial involving children receiving routine healthcare aged 2 to 4-5 years who are participating in the TARGet Kids! practice-based research network in Toronto, Canada. Children (N= 534) will be randomized to receive one of two interventions: 1) a recommendation to consume whole milk, or 2) a recommendation to consume reduced (1%) fat milk. The primary outcome is adiposity measured by Body Mass Index z-score (zBMI) and waist circumference z-score (zWC) 24 months post-randomisation; secondary outcomes will be cognitive development (using the Ages and Stages Questionnaire), vitamin D stores, cardiometabolic health indicators (glucose, hsCRP, non-HDL, LDL, triglyceride, HDL and total cholesterol, insulin, and diastolic and systolic blood pressure), sugary beverage and total energy intake (measured by 24-hour dietary recall), and cost effectiveness. Outcomes will be compared using ANCOVA, adjusting for baseline measures.

Ethics and dissemination: Ethics approval has been obtained from Unity Health Toronto and The Hospital for Sick Children. Results will be presented locally, nationally and internationally and published in a peer-reviewed journal. The findings may be helpful to nutrition guidelines for

children in effort to reduce childhood obesity using a simple, inexpensive and scalable cow's milk fat intervention.

Registration: This trial has been registered at clinicaltrials.gov (ID: NCT03914807).

6.2 BACKGROUND

Inexpensive and widely accessible cow's milk has been a dietary staple for children in North America for over a century. The majority of North American children consume cow's milk on a daily basis.[58,67] Cow's milk provides children with nutrients for growth and development such as protein, carbohydrates, calcium, vitamins A and D, and fat. The National Health Service,[54] Canadian Paediatric Society[304] and the American Academy of Pediatrics[629] recommend whole (3.25% fat) cow's milk for children beginning at 1 year of age to support optimal development in a period of rapid growth and high energy demand.[3,60] In an effort to curb childhood obesity, children are recommended to transition from whole to reduced fat (1% or 2%) cow's milk starting at 2 years of age.[54,304,629] However, this recommendation is based on low quality evidence (GRADE[594] score of 0-1)[15] derived primarily from consensus opinion.[15,630]

It is unclear whether switching from whole milk to reduced fat milk at age 2 years is beneficial. Observational evidence supports that children who consume whole milk have a lower risk of overweight or obesity relative to children who consume reduced (0.1-2%) fat milk.[4,7,563] A systematic review and meta-analysis of observational evidence for the relationship between cow's milk fat and child adiposity reported that children who consumed whole milk had 1/3 lower odds of overweight and obesity compared to children who consumed reduced (0.1-2%) fat milk.[631] Proposed mechanisms include higher satiety offered by whole milk due to hormonal responses to dietary milk fat consumption[21,563] thus displacing nutrient-poor foods or sugary beverages. Fatty acids found in cow's milk, such as trans-palmitoleic acid and conjugated linoleic acid, may be protective against excess adiposity.[22,27] Reverse causality could also explain this relationship, where parents may choose milk with a fat content to counter-balance the adiposity of their child (i.e. higher fat milk for a leaner child and vice versa).[82] Given the financial burden of overweight and obesity on healthcare systems worldwide,[632] determining which milk fat recommendation in childhood is effective in lowering a child's risk of developing excess adiposity, may result in substantial healthcare savings in the future.

It is possible that cow's milk fat may also result in other beneficial health effects. Higher circulating levels of trans-palmitoleic acid have been associated with lower adiposity, LDL cholesterol, insulin resistance, and triglycerides, and positively associated with HDL cholesterol, in several large adult cohort studies.[22-25] During early childhood, dietary fat consumption is known to support cognitive development, which usually concludes around six years of age.[266] Cow's milk fat may support brain development due to its essential fatty acid content (e.g. linoleic acid) which may manifest in gains across multiple developmental domains including social, emotional, and physical.[127,633] The ratio of essential fatty acids linoleic to alpha-linolenic acid (n-6 to n-3) in whole cow's milk is within the recommended ratio for DHA synthesis,[268] which is an important fatty acid for brain growth and function.[269]

Parents and clinicians, who rely on different nutrition information resources such as primary healthcare recommendations, have expressed interest in evidence-based guidelines for milk fat during early childhood.[634] Both whole and reduced fat milk are currently recommended to families with young children receiving primary healthcare.[634] To inform clinical practice and evidence based guidelines, randomized controlled trial evidence is needed to determine whether switching to reduced fat milk at 2 years of age or continuing with whole milk beyond 2 years of age results in improved growth, cardiovascular and cognitive developmental outcomes.

6.3 OBJECTIVES

Overall Objective: To determine whether a primary healthcare recommendation for whole (3.25% fat) vs. reduced fat (1% fat) milk in early childhood can: (1) reduce adiposity; (2) improve cardiovascular health; (3) improve cognitive development; (4) increase vitamin D stores and (5) reduce sugary beverage consumption and total energy intake at 24 months post-randomisation.

Hypotheses: We hypothesize that recommending whole milk between 1 and 4-5 years of age vs. transitioning to reduced fat milk at 2 years will result in the following outcomes at 24 months post-randomisation:

- ***Primary Outcome*:** Lower excess adiposity measured by: (a) body mass index z-score (zBMI) and (b) waist circumference z-score (zWC).
- ***Secondary Outcome 1:*** Lower risk of cardiovascular disease measured by: blood pressure, non-high density lipoprotein (HDL), low density lipoprotein (LDL), triglyceride, HDL and total cholesterol, glucose, insulin, high-sensitivity c-reactive protein (hsCRP), and glycosylated hemoglobin (HbA1C).
- ***Secondary Outcome 2:*** Higher vitamin D status measured by serum 25-hydroxyvitamin D (25(OH)D).
- ***Secondary Outcome 3:*** Better cognitive developmental scores measured by the *Ages and Stages Questionnaire* and the *Early Development Instrument*.[635]
- ***Secondary Outcome 4:*** Lower sugary beverage consumption and total energy intake measured by the Automated Self-Administered 24-Hour Recall tool (ASA-24).
- ***Secondary Outcome 5:*** Lower financial costs to both families and the health care system.

6.4 STUDY DESIGN AND METHODS

This will be a pragmatic, parallel group, superiority, randomised controlled trial. The study will include two active arms: 1) primary healthcare recommendation to consume whole milk starting at 2 years of age, and 2) primary healthcare recommendation to consume reduced fat (1%) milk starting at 2 years of age. This protocol has been designed following the 2013 SPIRIT guidelines[636] and registered at clinicaltrials.gov (ID: NCT03914807). Trial results will be reported according to the CONSORT guidelines for pragmatic trials.[637]

Study Setting

Healthy children aged 1.5 to 2.99 years will be recruited during a routine well-child doctor's visit at 12 participating *TARGet Kids!* academic pediatric or family medicine group practices in Toronto and Montreal over two years. The *TARGet Kids!* primary care research network and children's longitudinal cohort study is a collaboration between academic health outcome researchers at the University of Toronto, McGill University and a network of over 100 university affiliated primary healthcare providers (www.targetkids.ca).[638] Children participating in *TARGet Kids!* provide anthropometric, lifestyle, and developmental information and a blood sample at routine well-child visits. Recruitment started in February 2020 and is expected to take 24 months to complete enrollment.

Inclusion Criteria

Children who are: 1) healthy by parental report (characterized as not living with chronic or acute illness, except for asthma); 2) 1.5 to 2.99 years of age; 3) involved in a *TARGet Kids!* academic paediatric or family medicine group; 4) are from families with verbal communication in English or French.

Exclusion Criteria

Children who: 1) have Prader-Willi syndrome or other syndrome associated with obesity; 2) have severe developmental delay which impacts daily functioning; 3) are considered failure to thrive (children with zBMI values ≤ -2 are unlikely to benefit from obesity prevention); 4) are siblings of trial participants as families may share milk; or 5) do not consume cow's milk by choice, lactose intolerance or allergy.

Interventions

During a scheduled well-child visit, children aged 1.5-2.99 years will be randomized to one of two interventions currently provided in primary care:[634] 1) Whole fat milk recommendation, 2) Reduced fat milk recommendation (Figure 7). Standardized training sessions based on current clinical guidelines will be provided to participating primary care providers with quarterly reminders to ensure consistency in the provided recommendations. For children randomised to either group, research assistants will notify the child's physician of their allocated recommendation immediately prior to the clinical encounter. All participating healthcare providers have provided consent to participate in the randomization process. Intervention scripts for physicians can be found in *Appendix 8.3: Interview Scripts*.

Whole Milk Recommendation

Children randomized to the whole milk recommendation will receive a primary care recommendation to consume 500 mL of whole fat (3.25%) milk per day instead of transitioning to reduced fat (1%) milk at 2 years of age. Parents will also be provided bi-monthly email reminders. Children who receive the whole milk recommendation will be provided with the same age-appropriate nutritional recommendations for foods other than cow's milk as children who receive the reduced fat recommendation as part of routine healthcare according to the Rourke Baby Record.[52]

Reduced Fat Milk Recommendation

Children randomized to the reduced fat group will receive a primary care recommendation to transition from whole milk to 500 mL of reduced fat (1%) milk per day once the child is two years of age (consistent with current guidelines). Parents will also be provided bi-monthly email reminders. Children who receive the reduced fat recommendation will be provided with the same age-appropriate nutritional recommendations for foods other than cow's milk as children who receive the whole fat recommendation as part of routine healthcare according to the Rourke Baby Record.[52]

Adherence

Multiple methods will be utilized to maximize adherence to milk recommendations: 1) Primary healthcare providers will be reminded to repeat milk recommendations at up to two subsequent well-child visits during study participation; 2) Research assistants will provide participants with reminder magnets specific to their allocation group (see *Appendix 8.4: Reminder Magnets*) after receiving milk fat recommendations from the physician; and 3) Participants will receive an email survey bi-monthly which will ask about the enrolled child's recent milk consumption and remind families of the milk fat recommendation provided to them (see *Appendix 8.4: Reminder Email Script*).

Baseline Participant Characteristics

The following baseline variables will be measured: age, sex, zBMI, z-height, birth weight, waist circumference, ethnicity, maternal age and education level, duration of breastfeeding, current and past vitamin D supplementation, daily volume of cow's milk intake, daily multivitamin use, parental BMI, screen viewing time, physical activity, sleep time, and total dietary intake in the past 24 hours using the standardized *TARGet Kids!* data collection instrument adapted from the Canadian Community Health Survey:[639] Cognitive development will be measured using the Ages and Stages Questionnaire.[635]

Follow-Up Outcome Measures

Follow-up of parents and children will occur at 24 months post-randomization, which has been used in previous childhood obesity prevention trials.[640,641] Follow up will be completed by trained research assistants at each practice site during routine healthcare using the same techniques as baseline.

Primary Outcome

The primary outcome will adiposity, measured by the mean difference in age- and sex-standardized BMI z-score (zBMI) which will be measured at 24 months post-randomization. BMI z-score is an important outcome that is predictive of adiposity in later childhood, adolescence and adulthood.[642,643] Using standardized anthropometric protocols,[644,645] trained research assistants will measure children's height using a Healthometer stadiometer (Healthometer, Boca Raton, FL, USA) and weight will be measured using a digital Healthometer scale (Healthometer, Boca Raton, FL, USA). Body Mass Index (BMI) will be calculated as weight (kg) divided by height (m^2). Waist circumference (WC) z-score will also be used to assess adiposity, and will be measured by trained research assistance according to standardized anthropometric protocols.[644,645] Waist circumference has been associated with future weight gain, diabetes and cardiovascular disease and is the recommended measure for children with obesity.[646-649] Both BMI and WC will be standardized using the WHO growth references ranges (zBMI and zWC)[345,587] which reflect optimal childhood growth and are recommended for clinical use in Canada.[650] Velocity of zBMI change (from baseline to trial termination), which is predictive of higher BMI in adolescence and adulthood, will be used to measure differences in growth rate.[362,643]

Secondary Outcomes

Cardiovascular Health: Laboratory measures including glucose, hsCRP, non-HDL, LDL, triglycerides, HDL and total cholesterol, insulin, and diastolic and systolic blood pressure will be obtained since these measures track from childhood to adulthood and are important early indicators of cardiovascular health.[651-654] Non-fasting blood samples will be taken during the clinic visit by *TARGet Kids!* research assistants who are trained phlebotomists. Non-fasting measures have been established as equivalent to fasting measures, which are not feasible from young children.[296] Existing pediatric reference standards will be used to identify high risk children or the 90th percentile when these are unavailable.[655]

Vitamin D: Vitamin D will be measured by serum 25-hydroxyvitamin D concentration in nmol/L from venous blood at baseline and follow-up using isotope dilution liquid chromatography tandem mass spectrometry[656] by the Mount Sinai Services (MSS) Laboratory (mountsinaiservices.ca).[657]

Child Cognitive Development: Child cognitive development will be assessed by parental report using the *Ages and Stages Questionnaire (ASQ)*[635] at enrolment and follow-up visits. The *ASQ* is a parent completed developmental questionnaire which has been cross-culturally validated and is routinely used during primary healthcare as recommended by the American Academy of Pediatrics. It identifies children at risk of developmental delay across five domains: communication, gross motor, fine motor, problem solving and personal social behaviour. In addition, the junior and senior kindergarten teacher completed *Early Development Instrument (EDI)* will be collected in both junior and senior kindergarten to assess overall child development and school readiness. The EDI is collected across Canada for population-level monitoring of child development and covers 5 developmental domains: physical health and well-being, social competence, emotional maturity, language and cognitive development, communication skills and general knowledge.[658-660]

Sugary Beverage and Total Energy Intake: The Automated Self-Administered 24-hour Assessment (ASA24) from the National Cancer Institute of the National Institutes of Health will be used to measure sugary beverage and total energy intake at baseline and follow-up.[661] The ASA24 is a web-based tool that allows 24-hour food recall modeled after the USDA's Automated Multiple-Pass Method. The ASA24 has been validated for sugary beverage and total energy intake and has been piloted in Ontario children aged 2-5 years for feasibility of completion within 30 minutes.[661-663]

Sample Size

Previous obesity prevention trials have established a clinically meaningful zBMI difference of ≥0.25.[664,665] To detect this difference, 426 children will be required (n= 213 per group), based on an alpha of 0.05 with 80% power. To accommodate 20% loss to follow-up,[666] 534 1.5-2.99 year old children will be recruited (n= 267 per group) over 2 years and subsequently followed for 2 years.

Recruitment

Recruitment strategies include recruitment in person by a trained research assistant who is known to families through the TARGet Kids! program at a routine primary healthcare visit and collecting non-invasive measures (questionnaires and anthropometric measures) while the child and family wait for their primary healthcare provider visit.

Randomization

Children will be randomized using a 1:1 allocation ratio to either group. Randomization will be computer generated with variable block sizes, and will be stratified by site to ensure a balanced distribution of participants between groups within each of the sites.[667] Web-based central randomization will be utilized to preserve allocation concealment. After a child has been determined eligible to participate in CoMFORT and parents provide informed consent, research assistants will access the online central randomization system to ascertain the child's randomization status.

Blinding

Due to the nature of the study, children and parents cannot be blind, but they will be blind to the trial hypotheses. Primary healthcare providers who provide the recommendations also cannot be blind. Allocation concealment will be preserved for research assistants and parents who may enroll participants depending on randomization sequence if they are aware of it.

Retention & Complete Collection of Data

Every reasonable attempt (including phone calls and emails) will be made to locate CoMFORT subjects at follow-up. All families will be reminded via phone call to attend their scheduled annual well-child visit, consistent with routine practice. To further reduce loss to follow-up, parents who have moved out of district will be offered to visit The Hospital for Sick Children for repeat laboratory, cognitive and anthropometric testing.

Data Management

The Applied Health Research Centre (AHRC) of the Li Ka Shing Knowledge Institute of St. Michael's Hospital and Peter Gilgan Centre for Research and Learning of The Hospital for Sick Children will be the data coordinating centres. Study data were collected and managed using REDCap electronic data capture tools hosted at St. Michael's Hospital.[668] REDCap (Research Electronic Data Capture) is a secure, web-based application designed to support data capture for research studies, providing: 1) an intuitive interface for validated data entry; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for importing data from external sources. Laboratory tests from the Mount Sinai Services Laboratory will be directly uploaded through a secure web portal.

Statistical Analysis

Descriptive statistics for baseline characteristics (frequencies and proportions for discrete variables; means and standard deviations for symmetric variables; and, medians and inter-quartile ranges for skewed data) will be used to evaluate randomization completeness. The intent-to-treat principle will be applied to the analysis of outcomes.[669,670] Although randomization is expected to balance the covariates, variables that demonstrate, by chance, a potentially clinically meaningful imbalance, will be considered as adjusting covariates. For the primary analysis, zBMI at 24 months post-randomization will be compared between groups using ANCOVA adjusting for baseline zBMI. Because zBMI is age standardized, minimal differences in age at follow-up will be accounted for. For the secondary analyses, group differences in cognitive developmental scores, serum 25-hydroxyvitamin D concentration, cardiometabolic factors, sugary beverage and total energy intake will be compared using linear regression. Piecewise linear mixed models will be used to determine differences in growth rates between groups.

Cost Effectiveness

An economic analysis will be conducted to determine the incremental costs (or cost-savings) of whole vs. reduced fat cow's milk in reducing childhood adiposity, from both health system and societal perspectives. The time horizon will be limited to 5 years to leverage patient level data and minimize uncertainty from modelling a longer time horizon. All costs, parameter estimates and ranges will be derived from study data and will be obtained using medical record extraction. Publicly available Ontario costing sources will be used to cost resource utilization parameters. Cost-effectiveness will be expressed as the incremental cost-effectiveness ratio (ICER), calculated by dividing the incremental costs between the intervention arms by the incremental change in child's zBMI between baseline and the end of the follow up period. Costs will be adjusted for inflation using the Canadian Consumer Price Index and reported in 2022 Canadian dollars. An extensive one-way deterministic sensitivity analysis will be performed to evaluate the robustness of the results and evaluate uncertainty in any of the assumptions. Ranges for the sensitivity analysis will be obtained from 95% confidence intervals generated from study data for each of the parameters. Probabilistic sensitivity analysis using Monte Carlo simulation will be used to further evaluate uncertainty and establish a point estimate and 95% confidence interval around the ICER. Economic evaluation analyses will be carried out through the Ontario Child Health SPOR SUPPORT Unit.

Ethics and Dissemination

Approval has been obtained for the CoMFORT trial from the Unity Health Toronto (REB# 18-369) and Hospital for Sick Children (REB# 1000063023) Research Ethics Boards. Findings will be disseminated directly to primary healthcare providers and to parents. A meeting of all the *TARGet Kids!* practices, research team, and policy leaders (representatives from the University of Toronto Section of Community Paediatrics, Family and Community Medicine, Ontario Medical Association, Maternal, Infant, Child and Youth Research Network, College of Family Physicians, Canadian Paediatric Society, and parent representatives), and public health agencies (Public Health Ontario and Public Health Agency of Canada) will occur annually. Downstream dissemination to primary healthcare providers will occur through formal and informal avenues at local levels, such as City Wide Paediatric Rounds, national Continuing Medical Education events, and those held by local physician groups. Both parent and clinician members of the parent panel will play an integral role in communicating trial evidence by participating in the development of all dissemination material. End of grant knowledge will be shared with the academic community through multiple publications in a high impact journal as well as presentations at national and international conferences.

Consent

A stepwise proportionate consent model will be used for this study.[531] First, during the TARGet Kids! cohort study consent process, participants consent to be approached for additional research. As the second step, participants who consent to *TARGet Kids!* and are eligible for CoMFORT will be approached to participate in CoMFORT by research assistants at either the 18 month or 2 year well-child visit. Proportionate consent will be sought according to the National Health Service (UK) proportionate consent guidelines,[531] which have four components: providing a (1) verbal description of the study and (2) information sheet to participants, (3) answering participant questions, and (4) documenting informed consent.[531] *TARGet Kids!* research assistants will verbally provide information to each eligible family about the nature and purpose of the research, in addition to the material risks, benefits and alternatives, and provide an information sheet about the CoMFORT trial. Informed, written consent will then be obtained before randomization. A copy of the CoMFORT consent form can be found in *Appendix 8.4: Consent Form*.

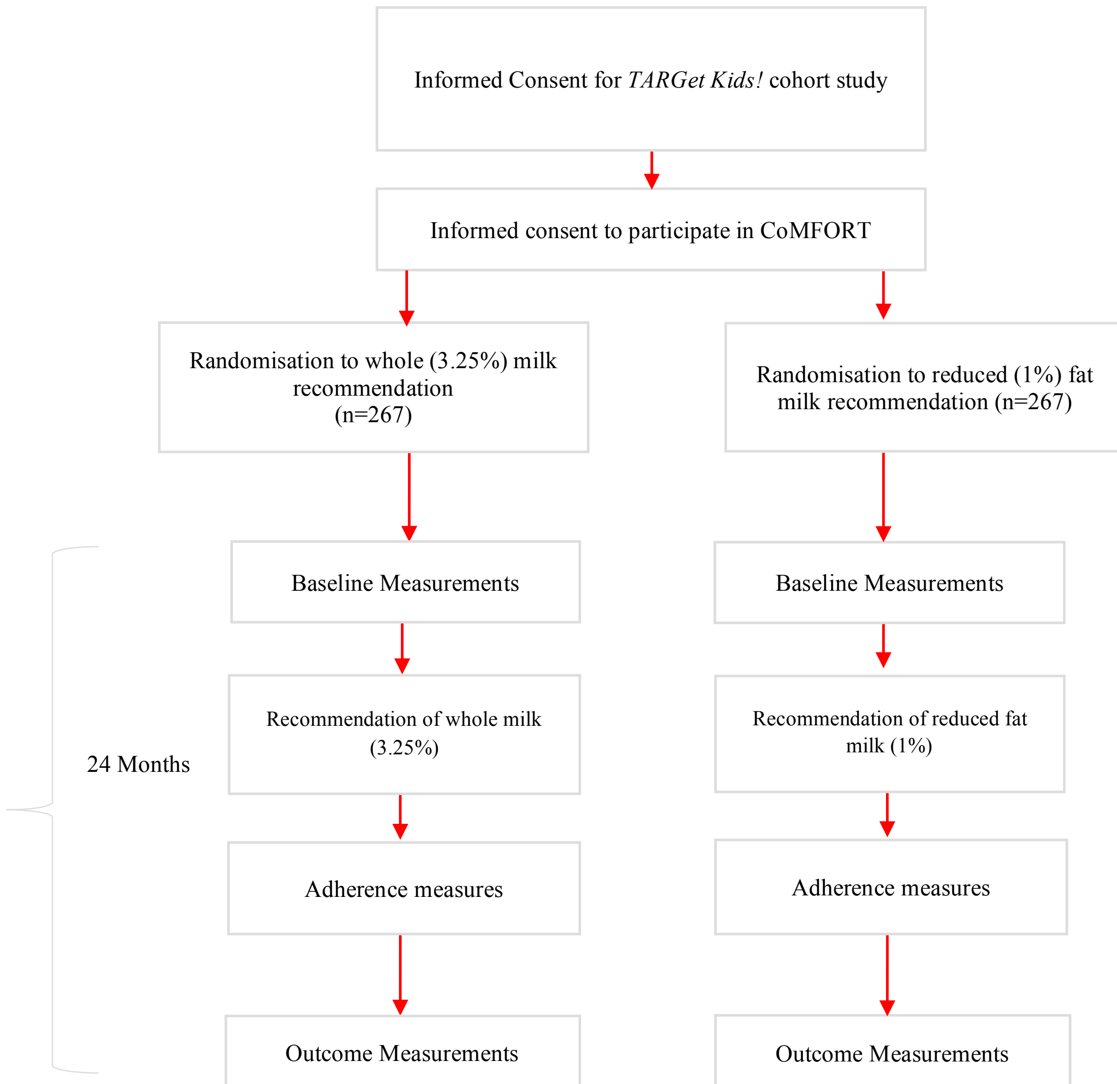
Patient and Public Involvement

Parents and clinicians identified this research question as important and relevant in a qualitative study using interviews and online questionnaires.[634] A *TARGet Kids!* parent panel informed all aspects of this protocol to maximally meet the needs of parents and children, including revising patient-facing materials about the intervention and consent forms, and guiding the design of the recruitment process. Parents verified the intervention as designed was appropriate and feasible. Over the course of this trial, the parent panel will meet virtually as needed and in person at least once every 6 months to discuss recruitment, study promotion, and overall progress. Parents' experiences will be valued as evidence and an integral part of the research process. Parent partners will contribute to knowledge translation strategies, co-author study publications and attend conferences alongside investigators to present study findings.

6.5 IMPACT

Results from this trial will be applicable to practice and nutrition guidelines because: 1) Two widely accepted, clinically relevant alternatives will be directly compared; 2) A diverse sample of healthy children participating in routine healthcare will be involved; 3) Practice settings representing the range of primary healthcare practice will be included (family medicine, primary care pediatrics, community health centres, etc.); 4) Patient-important health outcomes will be measured including adiposity, child cognitive development, and nutrition; and 5) The multidisciplinary team includes clinicians, parents, and policymakers as partners in the research process. The CoMFORT trial has been created through meaningful collaboration with parents through governance, conducting research, and knowledge translation. In doing so, the results of the CoMFORT trial will be well positioned for implementation and integration into the lives of children and families.

Figure 7. Trial flow diagram.



CHAPTER 7: OVERALL DISCUSSION

In this thesis, I have described the relationship between cow's milk fat and children's growth using multiple methods. I sought to: 1) Identify the relationship between cow's milk fat and child adiposity using data from the existing literature through a systematic review, 2) Understand parent and physician perspectives about cow's milk fat for children using qualitative methods, 3) Evaluate the longitudinal relationship between cow's milk fat consumption and child zBMI among children aged 9 months to 8 years of age using prospective cohort study methods, and 4) Design and launch an innovative randomized controlled trial to determine the effect of primary care recommendations for whole vs. reduced fat milk on zBMI among children aged 2 to 4 years. I hope that the research in this thesis will contribute to evidence-based nutrition recommendations for cow's milk during childhood. Nutrition guidelines on milk fat consumption for children have been based on consensus opinion and dated, poor quality information largely about safety, but not efficacy.[15,274,626]

7.1 Summary of principal findings in this thesis

Through a systematic review and meta-analysis of the existing evidence on the relationship between cow's milk fat and child adiposity, I screened over 5000 studies and identified 28 observational studies which had measured both milk fat consumption and adiposity in children. In 18 of the 28 included studies, higher cow's milk fat consumption was associated with lower child adiposity, 10 studies did not identify an association and no studies identified that higher cow's milk fat was associated with higher child adiposity. I subsequently conducted a meta-analysis on 14 of the 28 studies (N= 20,897) that measured the proportion of children who had consumed whole vs. reduced fat milk and provided direct measures of overweight or obesity. Among children who consumed whole (3.25% fat) vs. reduced fat (0.1-2%) milk, the odds ratio for overweight or obesity was 0.61 (95% CI 0.52 to 0.72, $p < 0.0001$), but heterogeneity between studies was high (I^2=73.8%). Although no clinical trials were identified, this study suggested that consumption of whole vs. reduced fat milk may not adversely affect body weight among children. To the contrary, higher milk fat consumption appears to be associated with lower odds of childhood overweight or obesity.

To understand parents' and physicians' beliefs about cow's milk fat for children, I conducted a qualitative study of parents and physicians participating in the TARGet Kids! cohort study. I determined that parents and physicians provide and recommend a variety of cow's milk fat for children, and hold mixed views of the role that cow's milk fat has on children's growth. Parents and physicians were similarly divided about providing or recommending whole milk or reduced fat milk for children 2 years of age or older. Through a thematic analysis of parent and physician interview transcripts, three themes were identified: 1) Healthy eating behaviours, which included the meaning of healthy food, who it is provided by and what it means to eat, provide, or recommend healthy food, 2) Trustworthy nutrition information, such as the trusted resources parents and physicians rely on to make decisions that affect the health of their children or patients, and 3) Importance of dietary fat for children, defined as the perception of dietary fat in children's diets, and what it means to provide fat to children. These themes were helpful in understanding how parents and physicians use trusted resources to develop healthy habits and behaviours, which informed perceptions about foods viewed as best for children's nutrition and development. This study helped to identify that there is equipoise in beliefs about milk fat among TARGet Kids! participating parents and physicians, and justify conducting a clinical trial in the TARGet Kids! environment for evaluating cow's milk fat recommendations in routine healthcare for children. It also reinforced the need for evidence-based recommendations about milk fat for children.

One of the limitations of the current literature which I identified in my systematic review was the lack of evidence from well controlled prospective studies and RCTs which accounted for clinically relevant factors such as volume of cow's milk consumed and parent BMI. I subsequently conducted a prospective cohort study involving 7,467 children aged 9 months to 8 years which identified that higher cow's milk fat consumption was associated with lower child zBMI after controlling for potential confounding factors including volume of milk consumed, parent BMI, and birth weight. Compared to children who consumed reduced fat (0.1-2%) cow's milk, there was evidence that children who consumed whole cow's milk had 16% lower odds of overweight (OR= 0.84, 95% CI 0.77 to 0.91, p< 0.0001) and 18% lower odds of obesity (OR= 0.82, 95% CI 0.68 to 1.00, p= 0.047). These findings were consistent with those identified in my systematic review and meta-analysis, and overcame a number of limitations presented by other observational literature including indirect measurement of adiposity, non-validated measures of exposures and outcomes, and cross-sectional designs. However, due to the observational nature of this study I was not able evaluate cause and effect and to what extent reverse causality, where parents of heavier children may provide lower cow's milk fat and vice versa, may have influenced findings. Together, this research highlighted the need for a randomized controlled trial to provide an unbiased evaluation of cause and effect.

To accomplish this, I have designed the Cow's Milk Fat Obesity pRevention Trial (CoMFORT), which will determine whether a primary healthcare recommendation for whole (3.25%) fat vs. reduced (1%) fat milk between the ages of 2 and 4 years can reduce zBMI and improve cardiovascular health in children at 4 years of age. The CoMFORT design was based on Trials within Cohorts methodology which aims to increase efficiency and generalizability of RCTs. With recruitment now underway, this study will include 534 children participating in the TARGet Kids! primary care research network in Toronto, Canada and provide numerous opportunities for advancing applied nutrition research. These include evaluating the causal connection between milk fat consumption and childhood adiposity and cardiometabolic health, evaluating patient engagement across trial development and conduct, analyzing the effect of a randomized lifestyle intervention embedded in usual care, and determining the feasibility of a proportional consent process which holds promise to lower barrier to clinical trial participation in a patient-centred way.

7.2 Clinical and public health importance of study results

Childhood obesity is one of the most important issues in child health with one in three children in Canada now overweight or obese.[671] Obesity in childhood increases the risk of sleep problems[672] and poor school performance in children and adolescents.[673-676] It also tracks into adulthood, increasing the risk of type 2 diabetes, cardiovascular disease and stroke.[677] It has long been known that life early nutrition is important for healthy growth, child development and lifetime success.[678] To date, successful interventions to prevent childhood obesity have been few in number and highly challenging to evaluate.

Cow's milk is consumed by the majority of children in North America. My overall aim was to generate evidence to help understand the relationship between cow's milk fat and children's adiposity. To address this, I conducted four studies which are included in this thesis. In my systematic review and meta-analysis, I found that international studies had, in general, found that higher cow's milk fat was associated with lower weight in children. These findings supported my previous findings and provided rationale and focus for further research in this area. In my prospective cohort study, I designed the analysis to address several limitations I observed among studies in the systematic review and meta-analysis by using linear mixed effects models and adjusting for covariates which might affect the relationship between cow's milk fat and child adiposity. My findings were consistent with those observed in the systematic review and meta-analysis, which added to the existing body of literature. In the qualitative study I conducted, I developed an understanding of how parents and physicians make decisions about milk fat and what sources of information were used to inform these decisions. This study helped guide future research on patients' values, beliefs and uncertainties about milk fat and was instrumental in guiding the design of the CoMFORT trial. Though the CoMFORT trial is not yet complete, I hope that its results will deepen our understanding of how cow's milk fat might influence child growth and cardiometabolic risk factors, as well as inform future innovative, patient-oriented clinical trials.

Existing obesity prevention clinical trials have been hindered by small sample sizes, high attrition rates and poorly representative populations.[372] Barriers to recruitment have involved factors related to children, parents, healthcare providers and the complexity of the interventions.[514,679] Children from diverse backgrounds tend to be unequally represented, making generalizability a challenge.[514,679] Unreasonable regulatory requirements, unpractical consent processes and ambiguous trial guidelines[680] have hindered the development of low risk trials of obesity prevention interventions. Family needs, preferences and resources are often not prioritized in the design of research or clinical practice guidelines.[500] These barriers present unique problems for generating evidence for early life nutrition interventions, where the success of the intervention in practice depends on its acceptability by healthcare providers and parents as well as accessibility, family resources and preferences.[681]

Innovative clinical trials have been proposed as a new method for advancing the evidence for healthcare interventions while overcoming limitations of traditional randomized controlled trials (RCTs) such as low recruitment rates, low efficiency, and poor generalizability.[682] During my

PhD, I designed and implemented a patient oriented innovative clinical trial called CoMFORT using novel Trials within Cohorts (TwiCs) methods.[682] CoMFORT will evaluate whether whole vs. reduced fat cow's milk is better for children. Through this process, I learned how to navigate solvable challenges to conducting clinical trials in children. I explored parent and clinician views and experiences about the study topic, which was an important first step to engaging families and ensuring that the intervention was relevant and acceptable.[634] Inviting parent partners to review the study protocol and consent process allowed us to prioritize patient preferences in study recruitment and intervention methods. Innovative techniques such as a brief and accessible consent form and using cohort study mechanisms to follow outcomes aims to lower barriers to participation and improved time- and cost-efficiency.[682] By partnering with families in all aspects of the research process, I aimed to earn their interest and trust, which is foundational to integrating trial results into clinical practice, nutrition guidelines, and the everyday decisions of Canadian healthcare providers and parents.[500,680]

Collectively, I hope that the research conducted through this thesis will assist policy makers in providing evidence based, age-appropriate and applicable information for organizations such as Health Canada and the Canadian Pediatric Society developing nutritional recommendations for cow's milk during childhood. Evidence-based recommendations about milk fat for children will help improve clinical practice and assist with the development of public health policies such as school lunch programs, and hopefully improve children's growth and cardiovascular health.

7.3 Strengths and limitations

7.3.1 Study-specific strengths

This thesis encompasses a body of research which has included several study designs in a thoughtful progression which included systematically evaluating the existing literature, understanding parent and healthcare provider perspectives, conducting a large prospective cohort study on cow's milk fat and child zBMI, and finally designing and implementing a clinical trial which aims to provide definitive evidence on cow's milk fat for child growth and nutrition.

In the systematic review and meta-analysis, I was able to include a large, diverse sample of children from around the world. The number of included studies was maximized by a comprehensive search strategy and contact with authors to obtain missing data. Study selection, data collection and risk of bias assessment were performed by two independent reviewers which improved accuracy and consistency of results reported. All studies included in the meta-analysis used trained individuals to obtain anthropometric measurements and weight status was standardized using growth reference standards (WHO, CDC and IOTF). Using sophisticated meta-regression techniques, differences in study design, risk of bias, and child age were taken into account. These techniques allowed a dose-response relationship to be demonstrated which showed a linear relationship between higher cow's milk fat and lower child weight.

In the qualitative study of parent and physician perceptions about cow's milk fat for children, recruitment took place in a primary care setting, which allowed me to obtain a sample of participants highly relevant to my research questions. Semi-structured interviews were informed by a quantitative questionnaire that provided focus and facilitated the identification of perspectives and ideas, which may not easily be captured by other research methods. The interviews allowed me to respond flexibly to participant responses, obtaining further details when appropriate, contributing to data richness. Data saturation was also considered to be reached, indicating a wide variety of viewpoints had been captured. Thematic analysis provided understanding of participant views and ideas which were directly related to my research questions and overarching concepts.

Strengths of the prospective cohort study included a large, diverse cohort of healthy children who were followed over many years and provided rich information about nutrition through early and middle childhood. A number of clinically relevant covariates which previous studies on this topic did not measure were controlled for, which reduced the risk of confounding. Complex statistical modeling using random effects models minimized within-subject correlation and improved model estimate accuracy. Restricted cubic splines allowed for evaluation of non-linear trends over time. Repeated measures data allowed me to estimate the directionality of this relationship, which improved upon the cross-sectional methods of previous studies by adding power and adjusting for within-subject measures.

7.3.2 Overall strengths

An overall strength is the relevance of the research topic to Canadian children, healthcare providers and families since childhood obesity is a pressing reality for many families[346] and cow's milk is consumed daily by the majority of Canadian children.[58] Though researchers have evaluated the relationship between cow's milk consumption and child adiposity in several previous studies,[382] the relationship between cow's milk fat intake and child adiposity was under-evaluated. My research was aimed at filling this important research gap and answering a question that is relevant to many healthcare providers and parents.[683]

I was able to analyze data from a large, diverse sample of children from around the world in order to describe a common relationship between cow's milk fat and child adiposity. Though many studies including those in the systematic review and meta-analysis and my study of TARGet Kids! participants adjusted for clinically relevant covariates, the ability to include children from unique communities in an array of geographical locations increased the probability that my findings were not spurious or confounded.

In each of the included studies, I was able to learn from experts in systematic reviews and meta-analyses, qualitative research, pediatric nutrition and obesity, innovative clinical trials, and biostatistics. This mentorship improved the scientific methods, depth, and overall quality of the research produced. For example, a talented research librarian, Naz Torabi, provided literature search methods expertise which assisted me in conducting the systematic review and meta-analysis, and helped make my literature search broad and systematically conducted. I was supported by Peter Jüni and Bruno da Costa who are experts in meta-analysis statistics, and Kevin Thorpe and Charles Keown-Stoneman, who are experts in clinical trials and observational study statistics, respectively. In my qualitative work, I was led by Clara Juando-Prats, who was essential in knowledgeably guiding me through transcript analysis and the development of themes. One other important group of experts I was able to work with was parents. Throughout the development of the CoMFORT trial I consulted parents of TARGet Kids! participants in every aspect of the trial design including as partners on the funding application. Collaboration with parents was important in ensuring that the topic was worthwhile for those it will impact, determining that the protocol and implementation strategy was acceptable to families with young children, and developing knowledge translation strategies.

7.3.3 Study-specific limitations

A limitation of my systematic review and meta-analysis was that all studies but one had high risk of bias. However, among studies in the meta-analysis, comparison of adjusted vs. crude odds demonstrated consistent findings. Heterogeneity was relatively high (I^2=73.8%) which may have been attributable to a variety of factors including varied methods of ascertainment of exposure and outcome, differences in study design, covariate adjustment and follow-up duration.

In the qualitative study, my views and perspectives may have introduced some biases to participant discussion, such as knowledge of clinical nutrition guidelines and current literature on children's nutrition. However, interview questions were reviewed by other researchers to mitigate risk of a biased script, and I kept a reflexive journal during the whole analysis, interpretation, and writing stages to minimize the projection of my views and thoughts. Although all parents who were approached to participate did so, participant views may be different than those of individuals who declined to participate in research activities, received or provide healthcare outside of *TARGet Kids!,* or did not have access to primary healthcare. However, data saturation was considered to be reached in the interviews, suggesting that many ideas were shared among participants in this study, which may be generalizable to populations outside of this study sample.

In the prospective cohort study, although cow's milk volume and sugary drink consumption were accounted for, there was insufficient data to calculate total daily energy which would have improved my understanding of the mechanism underlying the observed relationship. Further, cow's milk with different fat contents may have been offered to children based on parent perception of body size. Data on reasons for milk fat choices would have helped to clarify whether reverse causality contributed to the observed results, but this was not available.

7.3.4 Overall limitations

The observational nature of the studies in my thesis is an inherent limitation. Lack of RCT evidence identified in the systematic review did not provide sufficient evidence for me to assess the directionality or validity of the observed relationships. It was not possible for me to assess the contribution of reverse causality, where parents of leaner children may provide higher cow's milk fat and vice versa in either the meta-analysis or prospective cohort study. Though I was not able to demonstrate a causal relationship in my prospective cohort study, I generated child-specific splines which accounted for previous measures on the same child and provided a better estimate of directionality than previous cross-sectional studies. However, the cause and effect relationship between milk fat and child adiposity is still not clear, which provides justification for the CoMFORT trial.

Recall bias where foods consumed are poorly remembered, or social desirability bias where participants may report consuming foods they believe to be healthier are possible in observational nutrition research.[513] Food frequency questionnaires and 24-hour recalls used in studies included in the systematic review, as well as TARGet Kids! data collection are susceptible to misreporting or may not include specific varieties or quantities of foods actually consumed, leading to lower accuracy in understanding relationships between diet and health. Nutrition research which aims to understand pragmatic concepts embedded in everyday routines also faces challenges with these types of bias.[166] Further, parents or caregivers of young children may have difficulty completing dietary recalls on the child's behalf if meals are consumed at daycare or school and not monitored by the parent/caregiver. Standardized and validated dietary measurements are often used in nutrition research, but these are not always available and this may cause inaccuracies. In culturally diverse populations, ethnic foods may not be well captured by generic dietary recall tools. Within TARGet Kids!, the questionnaire used to capture dietary intake in children in the studies I have completed is based on the Canadian Community Health Survey.[684] However, children in TARGet Kids! aged 4 years and older are now able to complete the Automated Self-Administered 24-Hour Recall tool (ASA-24),[685] which is intended to improve the quality and accuracy of dietary data. This tool will be used in the CoMFORT trial at age 4 years.

Residual confounding is a limitation of observational studies, particularly those evaluating complex variables such as dietary intake and adiposity.[166] Though my prospective cohort analysis controlled for many factors known to be associated with dietary intake and adiposity, it is possible that other factors not captured influenced the relationship in ways I did not measure. For example, it would be useful to have better estimates of total daily caloric intake, timing of meals and snacks, and total daily energy expenditure, which may have helped to describe the mechanics of the relationship I observed. Other indicators of social determinants of health such as access to sufficient supply of fresh, nutrient dense foods and recreation programs and resources, as well as living environment would also be important to consider. Future studies will ideally gain a better understanding of such mechanisms with the use of accelerometers to measure physical activity and repeated 24 hour dietary recall measurements such as the ASA-24.

Error or imprecision in adiposity measurement may also have introduced bias to my studies. My prospective cohort study and all studies in my meta-analysis utilized trained personnel to take standardized measurements of participants to improve accuracy and reliability, but such measurements are still subject to errors, imprecision or data entry mistakes. My prospective cohort study used zBMI, which was standardized using the WHO growth standards, but other studies used different methods of adiposity measurement (i.e. body fat percentage, BMI), and different growth standards (i.e., IOTF or CDC) limiting comparability between them and possibly introducing bias. For example, use of the WHO rather than IOTF or CDC standards may have resulted in a greater proportion of overweight or obese children reported.[339] Future studies using WHO growth standards, which are believed to represent optimal child growth,[344] would help to minimize heterogeneity and overcome these limitations. Though zBMI is understood by families and physicians and is commonly used to track growth over time,[334] it is not a measure of body composition. Where possible, future studies would benefit from using measures such as dual x-ray absorptiometry (DXA or the Bod Pod) to gain a more precise estimate of body composition.

This research may not be applicable to other populations. Though children from nine countries (USA, UK, Canada, Brazil, Sweden, Spain, Greece, New Zealand, and Italy) were included in my systematic review, children from lower income countries, or other regions such as Asia were not represented. This is likely due to lower consumption of cow's milk in such areas relative to Western countries, which highlights the possibility that cow's milk interventions may not be applicable, feasible or acceptable to children and families elsewhere. Cultural and dietary norms may also limit the application of this research to other populations where traditional feeding practices may not include cow's milk consumption. In section 2.1.5 *Predictors of cow's milk consumption in children*, I outlined the possible influence of price and socioeconomic status on cow's milk fat choice for children. It has been noted that individuals of higher SES may be more likely to consume reduced fat cow's milk, which may be related to higher educational achievement and health literacy or access to nutrition recommendations, which encourage reduced fat dairy consumption.[686] However, though adults of higher SES are more likely to choose reduced fat cow's milk,[687,688] there is evidence showing that children of both low and high SES are likely to consume whole milk.[4,689-691]

7.4 Implications for clinical and public health practice

In 2019, the American Academy of Pediatrics, American Heart Association, Academy of Nutrition and Dietetics and other American health organizations created Healthy Beverage Consumption in Early Childhood recommendations.[692] These recommendations were informed by an expert panel, who conducted a scientific literature review and examined existing recommendations to determine consensus statements and recommendations. The aim was for recommendations in the final document to be based on the current best available evidence. For milk fat, the authors noted that, "the expert panel did not conduct a literature search on the heath impact of plain, pasteurized milk, as existing recommendations for young children's milk consumption are highly consistent."[692] I hope that research conducted through this thesis will assist policy makers with re-visiting current recommendations which, while consistent, may not be based on the best available evidence. Minimally, it is hoped that recommendations in the future will take into account that there is mixed evidence on this topic.

I suspect that my systematic review and meta-analysis generated attention[693,694] because this topic is of interest to parents. It may also have generated interest because the findings are not consistent with current global milk fat recommendations. I hope that this message is helpful in prompting future nutrition recommendations to include current research on milk fat. However, an important finding of my systematic review was that many included studies were low quality or had characteristics which rendered them high risk of bias. I hope that this will encourage researchers to conduct higher quality studies including longitudinal designs which account for important covariates, and clinical trials which are the best fair test of healthcare interventions. I provided an example of this through my prospective cohort study, which was informed by the limitations I observed in my systematic review and had findings which were consistent with those of the systematic review. In addition, the CoMFORT trial is an example of how a clinical trial, which was informed by patient views and uncertainties, could be conducted on this topic.

In my qualitative study, I showed that parents trust physicians and prioritize their advice over other sources of nutrition information for children. This is helpful to know as we begin to develop and communicate nutrition recommendations on this topic. It also shows how parents and physicians obtain and apply nutrition information to daily routines which informed the development of the CoMFORT trial.

Although cow's milk fat may be an aspect of childhood obesity prevention, it is likely only one small part of the broad, multi-factorial issue of childhood overweight and obesity. It is unlikely that any one preventive intervention such as the one tested in the CoMFORT trial will be a catch-all solution due to the complexity of child adiposity. Even when limited to nutritional factors, we know that one food or beverage is unlikely override the effect of other factors influencing the risk of overweight or obesity.[372] Many nutritional scientists agree that analyzing the entire diet is a comprehensive approach to understanding the relationship between food and health.[695] However, I suggest that cow's milk fat may be an important factor to consider when assessing children's dietary intake because many children consume cow's milk on a daily basis in quantities contributing up to 15% of daily energy intake.[63] The first years of a child's life are an opportune time for interventions to prevent chronic disease have long latency and can affect the entire life course. Therefore, should whole vs. reduced fat cow's milk demonstrate the potential to prevent childhood overweight or obesity in the CoMFORT trial, prioritizing this simple, scalable nutrition intervention may have impact in lowering the incidence of childhood overweight and obesity.

7.5 Future research directions

Randomized controlled trials are needed to understand the causal relationship between cow's milk fat and child adiposity in a variety of settings, communities, and populations. The CoMFORT trial will be an important step in a new body of literature on this relationship. Additional studies varying in pragmatic nature, mode of intervention delivery, and granularity of outcome measures will add important details such as the mechanism involved in the relationship between cow's milk fat and adiposity, how nutrition recommendations for children can best be communicated, and how adherence to nutrition recommendations might be sustained. Notably, an analysis of NHANES data was recently published (after my systematic review and meta-analysis) on the relationship between cow's milk fat and child adiposity in the USA, which had findings consistent with mine and highlights the generalizability and broad interest in this topic among other researchers and families.[419]

Routine clinical settings offer opportunities for conducting prospective observational nutrition research which engages diverse samples of individuals and follows them over long periods of time. Childhood is a unique opportunity for observational studies embedded in healthcare due to the frequency and consistency of well-child visits which are part of many healthcare systems. Despite the "gold standard" evidence provided by RCTs, prospective cohort studies offer a more pragmatic and less expensive (per person) approach to understanding dietary practices over a sustained period of time and may be less susceptible to attrition or non-compliance.[513] The original paradigm for RCTs was developed for pharmaceutical trials, which often involve a simple, controlled intervention, largely unaffected by unique or uncontrollable factors such as socioeconomic, behavioural and cultural variables.[513] In nutrition research, this methodology, which often involves isolating one factor in controlled environments, may not result in generalizable findings. Human nutrition is a dynamic, complex and long-term process. Teasing apart the relationship between specific foods and meaningful health outcomes is particularly challenging, especially during childhood when preferences change, new foods are frequently introduced and robust health outcomes are often distant in time. Ethical issues such as specifying control group conditions can also complicate RCTs in nutrition, whereas in free-living conditions it may be easier to assess natural gradients in dietary intake.[696] Pediatric nutrition RCTs are especially challenging to conduct due to stringent ethical concerns, small sample sizes owing to challenging recruitment processes, variable adherence to interventions and lack of long term follow-up. Each of these issues exacerbate problems such as poor quality and quantity of controlled trial data upon which create evidence-based paediatric guidelines. Lack of available evidence also frequently results in difficulties in demonstrating clinical equipoise which is a necessary condition for clinical trials to be conducted. This limits the potential to conduct new clinical trial research. Sometimes, this has led to the application of evidence from adult populations to child clinical and health policy guidelines as a last resort. This practice can be inappropriate and have unintended consequences due to the differences in physiology and metabolism between children and adults.[697]

Prospective cohort studies which are integrated within healthcare environments are increasingly used to generate the best available evidence in nutrition research. Such studies tend to include a diverse population (ideally all patients receiving care), minimize participant burden by using routine clinical methods for data capture and can follow individuals long-term through the health system. Such studies have potential to facilitate high quality, generalizable and relevant observational research, especially when patients are involved in determining research priorities and designing study methods and materials. Practice-embedded prospective cohort studies also lay a foundation for comparative effectiveness RCTs (for example, CoMFORT) where low-risk interventions take place in routine healthcare settings and outcomes are used that are already part of cohort study measures. An important step in facilitating such studies is for clinical research regulatory systems (i.e., REBs) to permit streamlined informed consent procedures which reflect the actual level of risk involved in comparing interventions which are already part of standard healthcare.[534,698] In addition, forming and collaborating with patient and family advisory panels can help to ensure research is relevant, applicable and feasible.[506]

More rigorous adiposity measurement tools (such as DXA) used in combination with biochemical values (such as serum cholesterol, triglyceride and glucose concentrations) may provide a more holistic assessment of cardiometabolic health, which may better capture modifiable factors that lower the risk of excess adiposity or other chronic disease through higher precision measurement. Biochemical markers of food intake could also be used to validate dietary recalls, such as serum pentadecanoic or heptadecanoic acid concentration to estimate dairy fat; however, these measures are expensive and relatively invasive as they involve blood testing.

Interventions which show the most promise in addressing childhood overweight and obesity have been focused on individual, family and community levels and include strategies for both physical activity and nutrition.[372] In order to further understand the multifactorial nature of child nutrition, growth and development, it is also important to conduct studies that capture a wide range of nutritional, biochemical, anthropometric and sociodemographic factors. This will allow researchers to perform sophisticated statistical analyses such as linear mixed effects models that take into account multiple factors simultaneously and over time. It will also increase efficiency by raising the amount of information gained from expensive and time-consuming clinical research studies. Though widely acceptable, effective and sustainable interventions are complicated to implement, determining strategies that positively impact child health in diverse populations over a sustained period of time is important for improving the effectiveness of 21st century healthcare and improving Canadians' quality of life.

7.5.1 Patient engagement

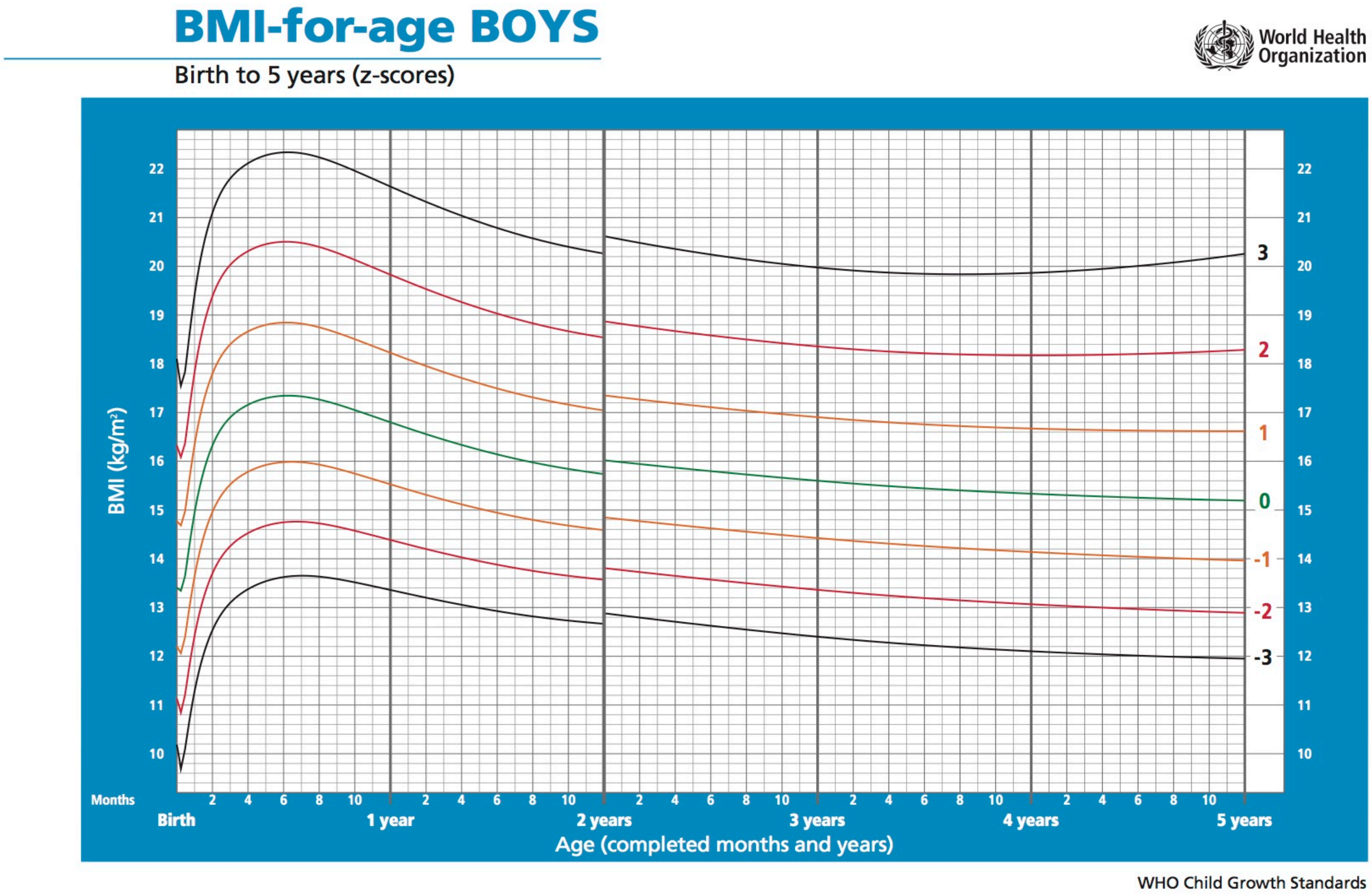
Patient oriented research is gaining popularity among North American researchers, and is well established in the UK.[699] As researchers increasingly include parents, caregivers and families in studies involving children, the goal is to impact healthcare such that there will be a wider variety of accessible and acceptable care options for families with diverse preferences and needs.[681] Ideally, this will create evidence for questions that are relevant to families and improve the quality of healthcare that children receive. When families and parents are involved in prioritizing, designing and implementing nutrition research, it is expected that new nutrition interventions which are implemented in practice might be more acceptable.[700] Future intervention studies which aim to improve children's nutrition may benefit from engaging families and caregivers early in the research process to ensure that the intervention is relevant and feasible. Input from families may assist with understanding how the intervention might fit with their preferences and daily routines, which may improve recruitment and retention, and make knowledge translation efforts at the end of the research process more effective.[500,701] Given these potential benefits, there is a need for guidance, evidence-based frameworks, evaluation, financial support, and expertise in patient-oriented nutrition research.[681]

7.6 Concluding remarks

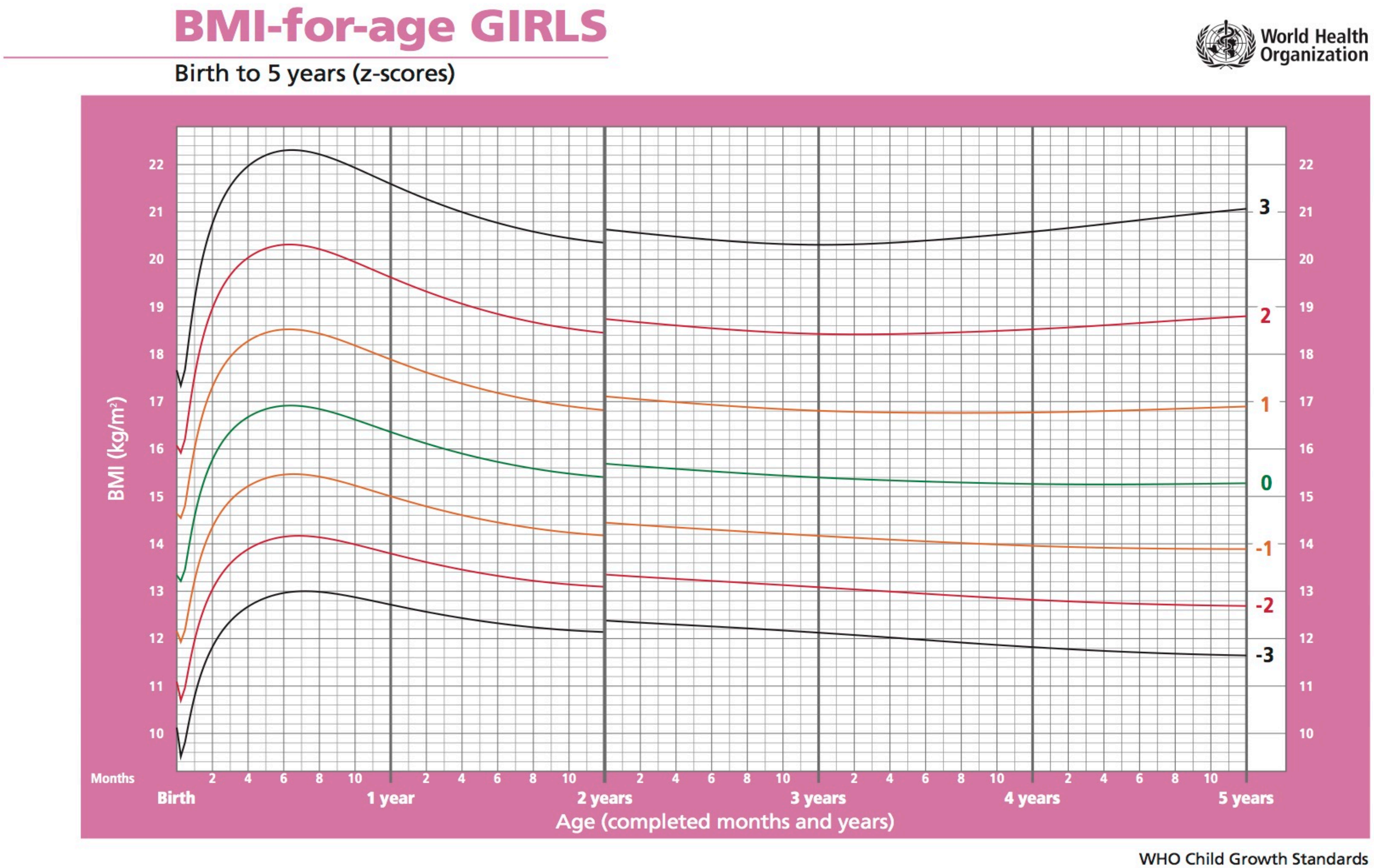
For decades, a recommendation for reduced fat cow's milk during childhood aimed at lowering children's risk of overweight and obesity has been part of clinical care and public health policy. Though this recommendation was based on expert opinion and was sensible at the time, systematic review evidence from this thesis has shown that existing research on the relationship between cow's milk fat consumption and childhood overweight and obesity is not consistent with this recommendation. Among 20,897 children who participated in observational studies from seven countries and were included in my meta-analysis, those who consumed whole cow's milk had lower risk of overweight or obesity than those who consumed reduced fat milk. Similarly, through my prospective cohort study, which accounted for clinically relevant covariates, I demonstrated similar findings. Through my qualitative research, parents and physicians expressed that this research is relevant and important for daily decision making. The CoMFORT trial will generate evidence describing the causal relationship between cow's milk fat and child adiposity, adding clarity to the current understanding of this topic. Collectively, the research conducted in this thesis provides new evidence to guide future research on the relationship between cow's milk fat and child adiposity. It is my hope that my research and the interventional research which will follow will be useful to health organizations worldwide when making cow's milk fat recommendations for children.

CHAPTER 8: APPENDIX

8.1 WHO BMI-For-Age Curves & Canadian BMI Growth Curves

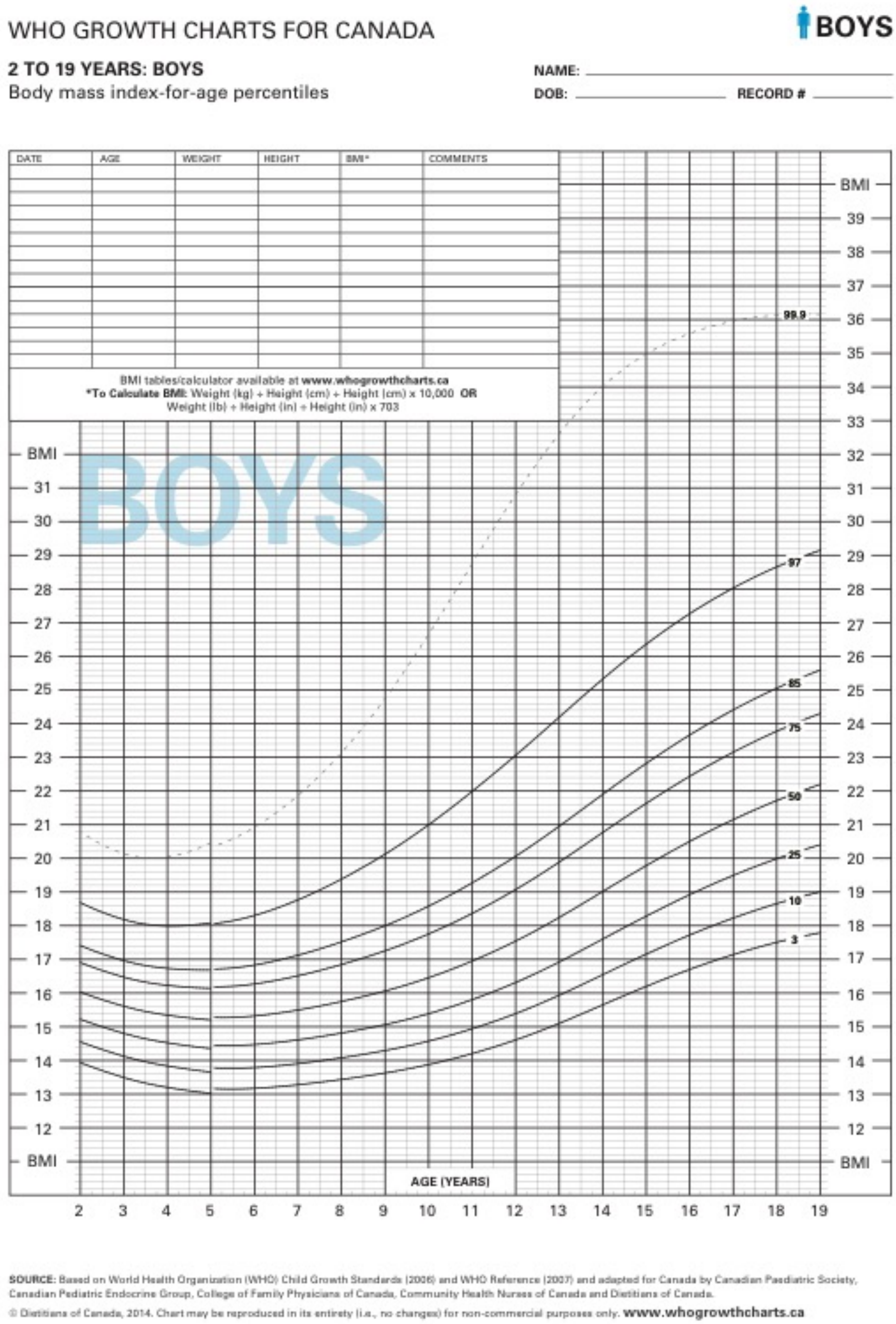


Source: World Health Organization [http://www.who.int/childgrowth/standards/cht_bfa_boys_z_0_5.pdf?ua=1]



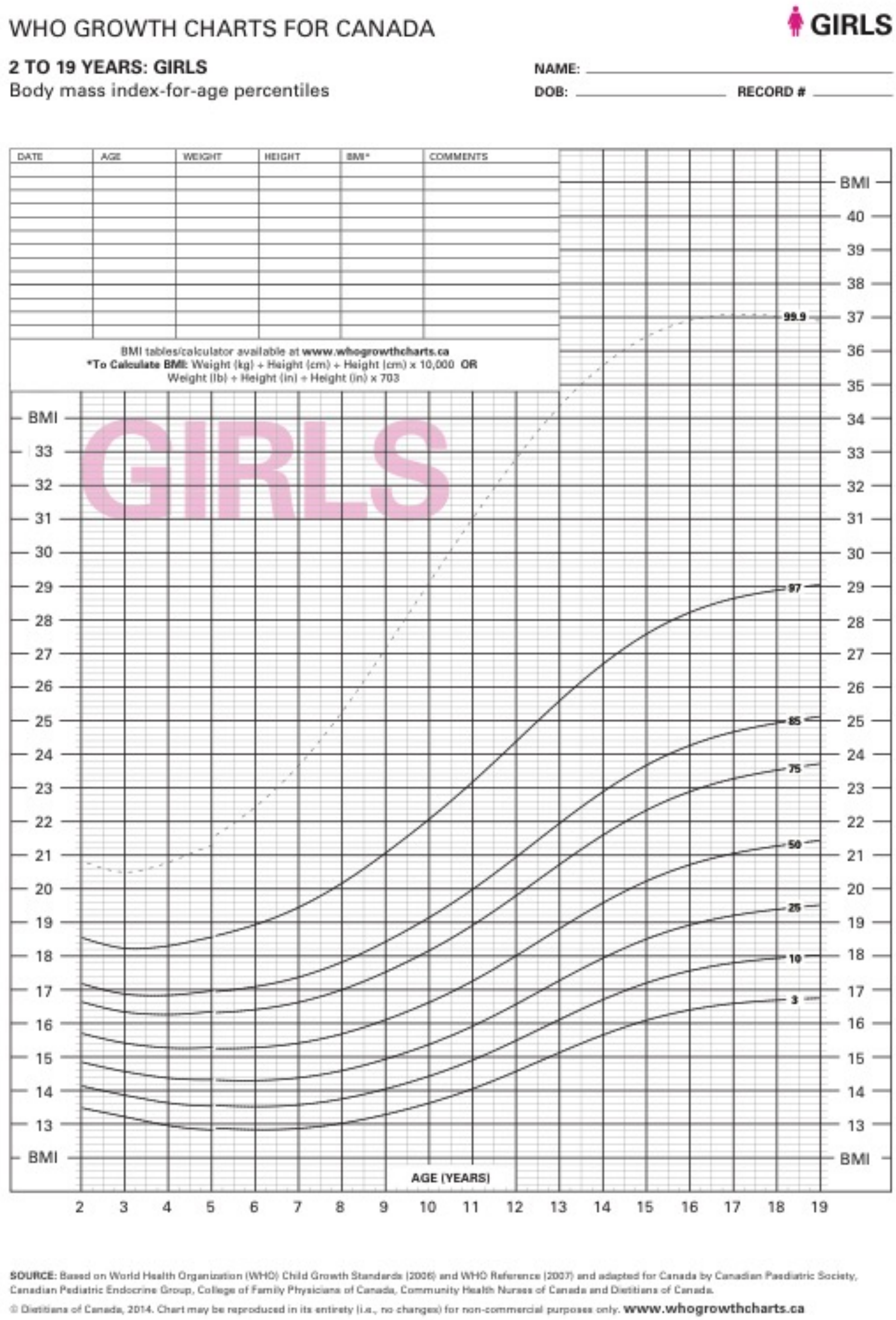
World Health Organization [http://www.who.int/childgrowth/standards/cht_bfa_girls_z_0_5.pdf?ua=1]

Canadian BMI Growth Curves: Boys



Dietitians of Canada
https://www.dietitians.ca/DietitiansOfCanada/media/Documents/WHO%20Growth%20Charts/Set-2-BMI_2-19_BOYS_Set-2_EN.pdf

Canadian BMI Growth Curves: Girls



Dietitians of Canada
https://www.dietitians.ca/DietitiansOfCanada/media/Documents/WHO%20Growth%20Charts/Set-2-BMI_2-19_GIRLS_SET-2_EN.pdf

8.2 Supplementary Material for Cow's Milk Fat and Child Overweight: A Systematic Review and Meta-Analysis

Table 1. Previous review article findings on dairy intake and child health outcomes.

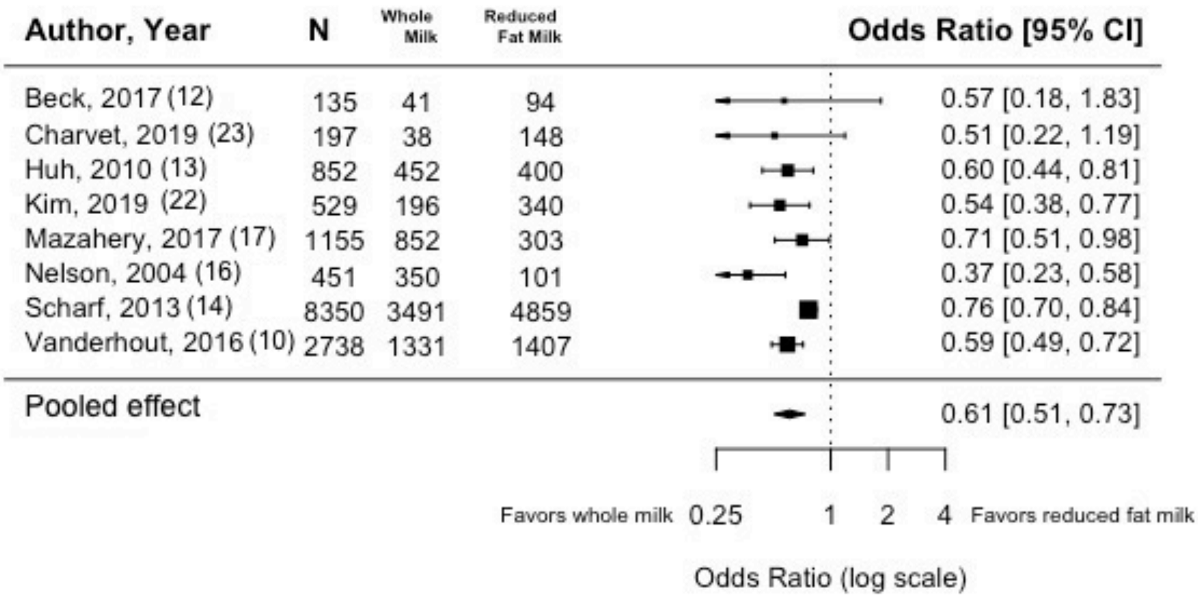
Author (year)	**Review type**	**Objective**	**Findings**
de Beer (2012) [246]	Systematic review and meta-analysis	Summarize controlled trials investigating dairy product intake and physical (linear) growth	There is moderate evidence from 12 (7 randomized, 5 non-randomized) trials to support dairy consumption for linear growth.
Dougkas (2019) [702]	Critical review	Evaluate available evidence on milk intake and the development of obesity in children and adolescents	Milk and dairy were not associated, or inversely associated, with obesity and indicators of adiposity in children. There was insufficient evidence that the relationship varied by type of milk or dairy product, or age of the children. Nine of 94 identified studies showed a positive relationship between milk and body fatness; the remainder showed inverse or neutral relationships.
Dror (2014) [223]	Narrative review	Evaluate health effects of milk consumption in children	Among 35 intervention and observational studies, only one RCT showed an inverse relationship between cow's milk intake and child adiposity. One observational study showed a positive association between milk intake and BMI. The remainder did not show evidence of a relationship between milk consumption and child health outcomes.
Griebler (2016) [703]	Systematic review and meta-analysis	Summarize short- and long-term health effects of cow's milk intake before age 3 years	Cow's milk intake during infancy was associated with iron deficiency. In one prospective cohort study, children aged 2-4 years who consumed more cow's milk had higher BMI. One RCT comparing follow-on formula to cow's milk found no difference in child growth.
Huang (2005) [704]	Narrative	Summarize dairy intake, obesity, and metabolic health in children and adolescents	Three observational studies showed evidence of a relationship between higher dairy intake and lower body fat; 5 observational studies and 10 RCTs showed no evidence of a relationship between dairy intake and adiposity.
Kang (2019) [382]	Systematic review and meta-analysis	Evaluate evidence of randomized controlled trials assessing whether milk consumption could affect growth and body composition among children and adolescents aged 6–18 years	Milk interventions resulted in a greater increase in body weight, lean mass, and attenuated gain in percentage body fat compared with control groups. There was no evidence of changes in fat mass, height, or waist circumference in the intervention groups compared with the control groups.
Kouvelioti	Systematic review	Examine RCTs on dairy	Dairy intake benefited bone structure and development, but did not appear

(2017) [247]		consumption and body size, bone composition and bone properties in children and adolescents	to affect body composition or body size. Two of 14 RCTs showed evidence of conflicting child weight outcomes, and 1/11 RCTs on body composition found evidence of an increase in lean body mass in response to higher cow's milk intake.
Louie (2011) [705]	Systematic review	Examine relationship between dairy consumption and overweight/obesity in prospective cohort studies	Of 10 studies identified in children, 3 showed evidence of relationships between higher dairy consumption and lower weight gain, 1 reported a positive association between dairy intake and weight gain, and the remainder did not show evidence of relationships.
Lu (2016) [706]	Systematic review and meta-analysis	Examine relationship between dairy consumption and risk of obesity in children	Among 10 studies, there was evidence that children who consumed the most dairy had a 38% lower risk of overweight or obesity than those who consumed the least.

Table 2. Results of meta-regression models showing the relationship between consumption of whole milk vs. reduced fat milk and odds ratio (OR) of overweight and obesity, including interaction terms for study design, adjusted vs. crude ORs, risk of bias and age group.

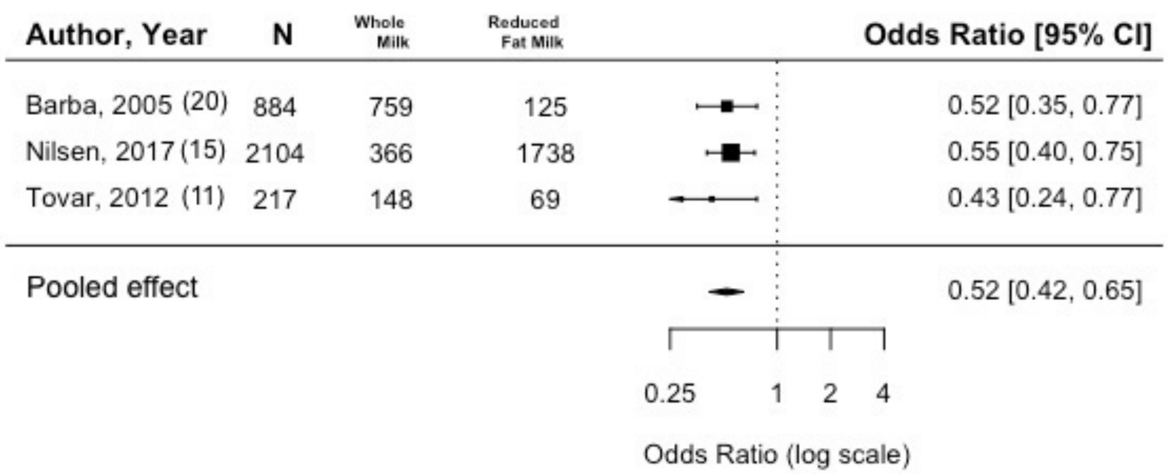
Factor	No. of studies	Odds Ratio (95% CI)	p value for interaction
Study design			0.07
Cross-sectional	11	0.56 (0.46 to 0.69)	
Prospective cohort	3	0.76 (0.63 to 0.92)	
Risk of Bias			0.92
Low	1	0.60 (0.44 to 0.81)	
High	13	0.61 (0.51 to 0.73)	
Age (years)			0.23
1-5	8	0.61 (0.51 to 0.73)	
6-11	3	0.52 (0.42 to 0.65)	
12-18	3	0.74 (0.41 to 1.35)	

Figure 1. Odds ratio of overweight/obesity comparing children who consumed whole milk vs. reduced fat milk among children aged 1-5 years.



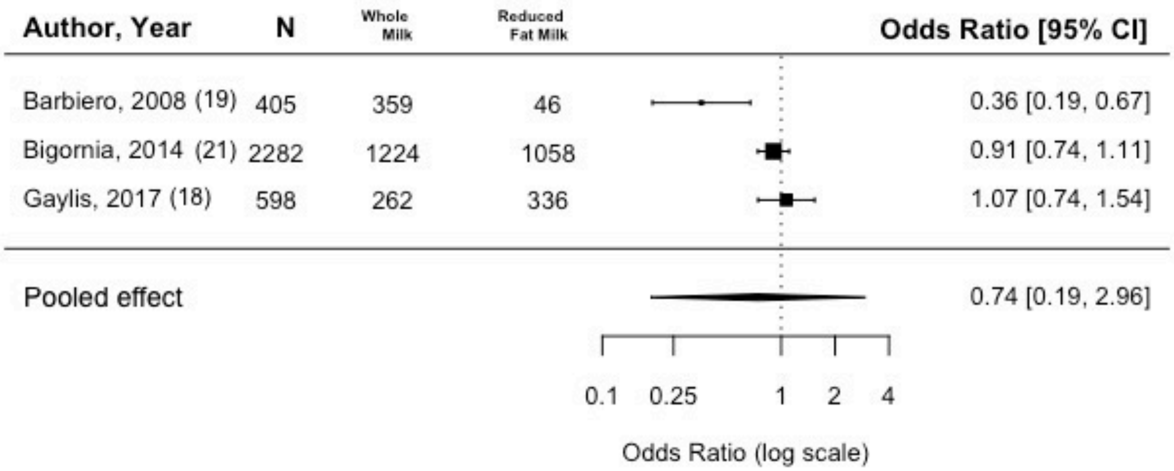
Pooled effects were determined using a random-effects model.

Figure 2. Odds ratio of overweight/obesity comparing children who consumed whole milk vs. reduced fat milk among children aged 6-11 years.



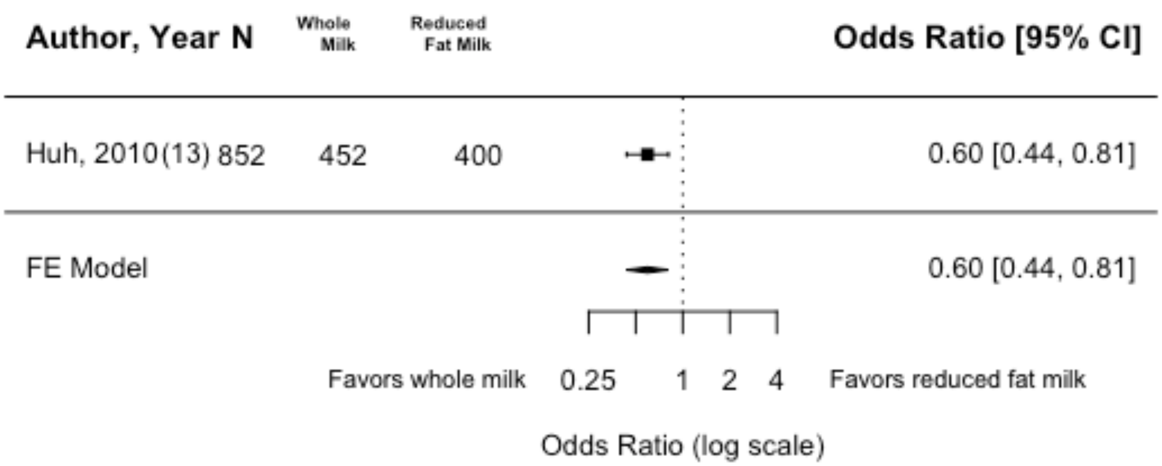
Pooled effects were determined using a random-effects model.

Figure 3. Odds ratio of overweight/obesity comparing children who consumed whole milk vs. reduced fat milk among children aged 12-18 years.



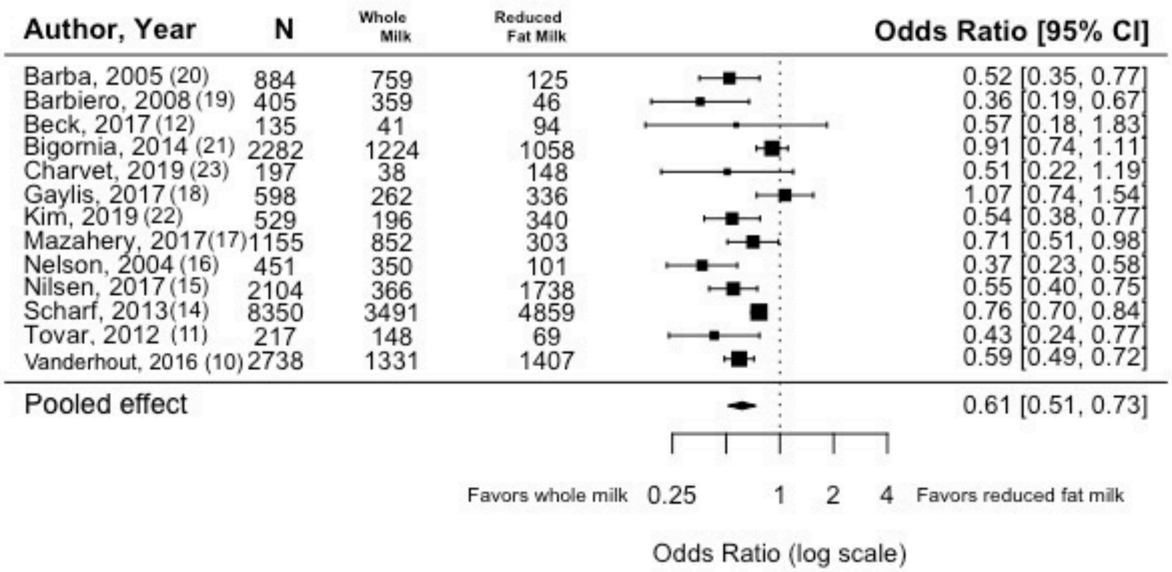
Pooled effects were determined using a random-effects model.

Figure 4. Odds ratio of overweight/obesity comparing children who consumed whole milk vs. reduced fat milk among low risk of bias studies.



*FE=fixed effects meta-analysis model.

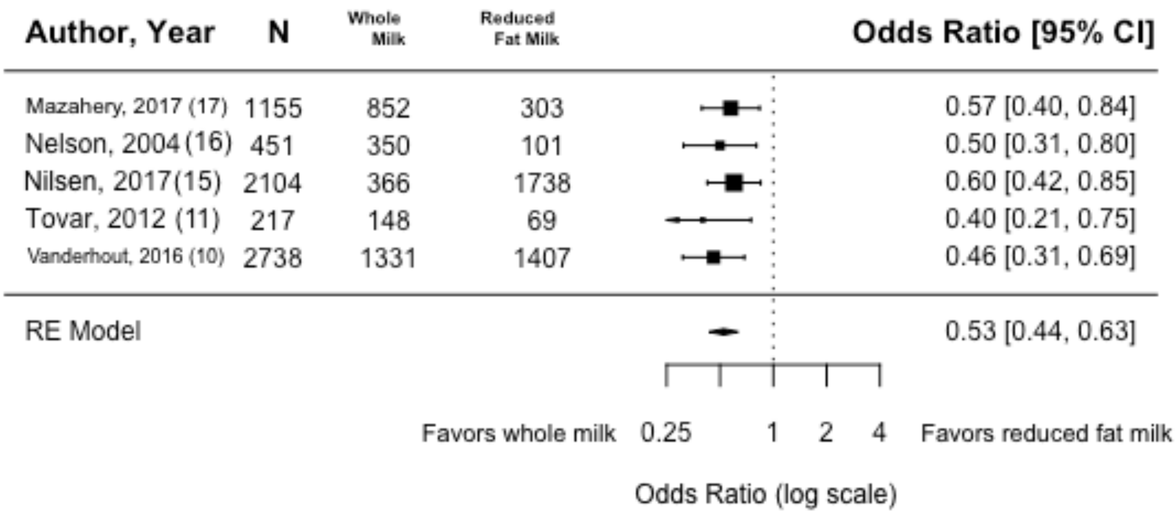
Figure 5. Odds ratio of overweight/obesity comparing children who consumed whole milk vs. reduced fat milk among high risk of bias studies.



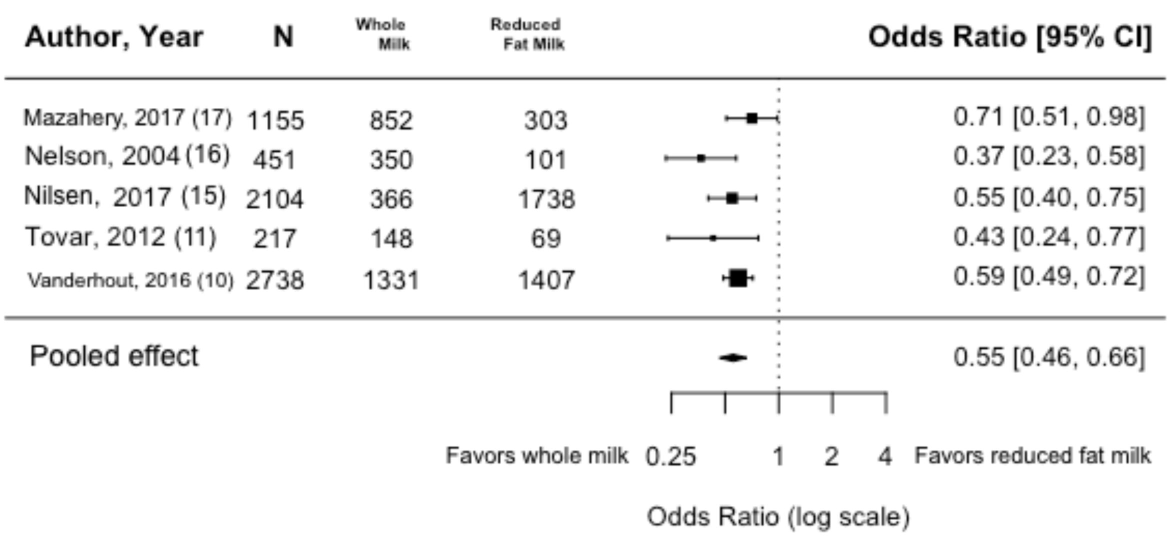
Pooled effects were determined using a random-effects model.

Figure 6. Reported, adjusted vs. crude odds ratios of overweight/obesity comparing children who consumed whole milk vs. reduced fat milk.

Panel A: Adjusted, reported odds ratios:

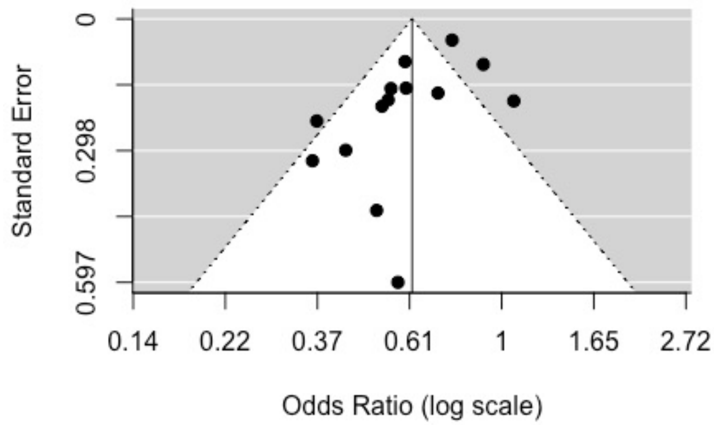


Panel B: Crude odds ratios:



Pooled effects were determined using a random-effects model.

Figure 7. Funnel plot for studies included in meta-analysis of consumption of whole milk vs. reduced fat milk and odds ratio (OR) of overweight and obesity.



Egger's test p= 0.04.

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8.3 Supplementary Material for A Qualitative Study to Understand Parent and Physician Perspectives About Cow's Milk for Children

REB Approval Letter

Research Ethics Office
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E-mail: pateld@smh.toronto.on.ca

St. Michael's
Inspired Care.
Inspiring Science.

May 2, 2018

Dr. Jonathon Maguire,
Department of Paediatrics,
St Michael's Hospital

Dear Dr. Maguire,

Re: REB# 18-077[C] - Optimizing the feasibility of the Cow Milk Fat Obesity pRevention Trial: CoMFORT

REB APPROVAL:	Original Approval Date	May 02, 2018
	Annual/Interval Review Date	May 02, 2019

Thank you for your application submitted on **28 February, 2018**. The above noted study has been reviewed through a delegated process (not by Full Board review). The views of the St. Michael's Hospital (SMH) Research Ethics Board (REB) have been documented and resolved. Please note that no member of the St. Michael's Hospital Research Ethics Board associated with this study was involved in its review or approval.

The REB approves the study as it is found to comply with relevant research ethics guidelines, as well as the Ontario Personal Health Information Protection Act (PHIPA), 2004. The REB hereby issues approval for the above named study for a period of 12 months from the date of this letter. Continuation beyond that date will require further review of REB approval. In addition, the following documents have been reviewed and are hereby approved:

1. Protocol - ver: 3 4/27/2018
2. Physician/Parent Survey Script ver: 3 4/27/2018
3. Parent/Physician interview script ver: 3 4/27/2018
4. Poster - ver: 2/27/2028

Furthermore, the following documents have been received and are acknowledged:

1. Interview Form - Phone Interview Landing Page ver: 3 4/27/2018
2. Process for documenting verbal consent for interviews ver: 3 4/27/2018
3. Master Linking Log - ver: 4/27/2018

During the course of this investigation, any significant deviations from the approved protocol and/or unanticipated developments or significant adverse events should immediately be brought to the attention of the REB. Please note that shared electronic health systems such as ConnectingOntario, PRO, RM&R, OLIS, HDIRS, eCHN, DPV and IAR do not permit access for research purposes.

All interventional trials where SMH is the Sponsor institution or where the lead Principal Investigator (PI) is at SMH are required to (1) register the study in a registry accepted by the International Committee of Medical Journal Editors (ICMJE) and World Health Organization (WHO), (2) ensure that the trial record is updated in a timely manner and (3) post summary results within the required timelines.

All institutional approvals **must be** coordinated and approved through the Office of Research Administration (ORA) prior to initiation of this research. If a Clinical Trial Agreement is required, it must be reviewed and approved by the ORA, prior to commencing any study related activities.

All investigational drug product dispensing must be coordinated through the Research Pharmacy at 416-864-5413.

The St. Michael's Hospital (SMH) Research Ethics Board (REB) operates in compliance with the Tri-Council Policy Statement Ethical Conduct for Research Involving Humans, the Ontario Personal Health Information Protection Act, 2004, and ICH Good Clinical Practice Consolidated Guideline E6, Health Canada Part C Division 5 of the Food and Drug Regulations, Part 4 of the Natural Health Product Regulations, and the Medical Devices regulations. Furthermore, all investigational drug trials at SMH are conducted by Qualified Investigators (as defined in the latter document).

With best wishes

☐ David Mazer, MD
Chair, Research Ethics Board

☐ Philip Berger, MD
Vice Chair, Research Ethics Board

☒ Michael Szego, PhD
Vice Chair, Research Ethics Board

DM/PB/MS/JL

Questionnaire Script

Online questionnaire script:

We are seeking 20 parent and 20 physician volunteers to participate in a web-based online questionnaire on cow's milk fat. It should take approximately 3 minutes to complete.

PARTICIPATION

Your participation in this questionnaire is voluntary. You may refuse to take part in the research or exit the questionnaire at any time without penalty. You are free to decline to answer any particular question you do not wish to answer for any reason. Due to the anonymous nature of the questionnaire, you are not able to withdraw responses once they are submitted.

[For parents] If you choose not to participate, you and your family will continue to have access to customary care at St. Michael's Hospital. If you choose to take part in this study, you can change your mind without giving a reason, and you may withdraw from the study at any time without any effect on the care you or your family will receive at St. Michael's Hospital.

[For physicians] The decision to participate or not, and the responses given, will have no impact on your position or evaluation at SMH.

BENEFITS

You will receive no direct benefits from participating in this research study. Your responses will help us learn more about your attitudes towards cow's milk fat and help us to develop a new clinical trial tailored to your needs.

RISKS

There are no foreseeable risks involved in participating in this study other than those encountered in day-to-day life and potential inconvenience of 3 minutes of your time.

CONFIDENTIALITY

Your questionnaire answers will be sent to a link at SurveyMonkey.com where data will be stored in a password protected electronic format. Survey Monkey does not collect identifying information such as your name or email address. Therefore, your responses will remain anonymous. No one will be able to identify you or your answers, and no one will know whether or not you participated in the study. Once analyzed for research purposes, data will be stored for 7 years, and then destroyed.

By completing this questionnaire, you are agreeing to the following: Since Survey Monkey's servers are located in the United States, they are subject to the conditions of the Patriot Act which allows authorities to access the records of internet service providers. If you choose to participate in this questionnaire, you understand that your responses to the questionnaire questions and IP address may be accessed outside of Canada.

ELECTRONIC CONSENT

Please select your choice below. You may print a copy of this consent form for your records. Clicking on the "Agree" button indicates that

- You have read the above information
- You voluntarily agree to participate
  - ☐ Agree
  - ☐ Disagree

Physicians:

1. What cow's milk fat recommendation do you typically make during the 2-year well-child visit?
    1. Skim (0.1%)
    2. 1%
    3. 2%
    4. Whole/homo (3.25%)

5. None

2. What dietary recommendations do you usually provide to parents of ~2 year old children whom you, or the parent, suspects is at risk of overweight/obesity?
    i. Reducing sugar sweetened beverage intake
    ii. Reducing bottle use
    iii. Reducing fat intake
    iv. Reducing fat content of cow's milk to skim, 1% or 2% fat
    v. Increasing fat content of cow's milk to 3.25% fat
    vi. Reducing caloric intake
    vii. Increasing fruit/vegetable intake
    viii. Structuring meals/snacks
    ix. Other (please specify)
3. What dietary recommendations do you usually provide to parents of ~2 year old children whom you, or the parent, suspects is underweight?
    i. Increasing energy intake
    ii. Increasing fat content of cow's milk to 3.25% fat
    iii. Reducing fat content of cow's milk to skim, 1% or 2% fat
    iv. Increasing meal/snack frequency
    v. Food fortification (i.e. protein powders)
    vi. Other (please specify)
4. What do you think is the ideal cow's milk fat content children over 2 years of age to consume?
    i. Skim (0.1%)
    ii. 1%
    iii. 2%
    iv. Whole/homo (3.25%)
5. What do you think are the benefits of providing children older than 2 years of age with whole (3.25% fat) milk (select all that apply)?
    i. Better body composition
    ii. Healthier growth rate
    iii. Better brain development
    iv. Obesity prevention
    v. Better nutrition (fat soluble vitamins etc.)
    vi. Other (please specify)
    vii. None
6. What do you think are the harms of providing children older than 2 years of age with whole (3.25%) fat milk (select all that apply)?
    i. May cause higher adiposity
    ii. Higher saturated fat intake
    iii. Creation of higher fat dietary pattern
    iv. Other (please specify)
    v. None
7. What do you think are the benefits of providing children older than 2 years of age with reduced (1% or 2%) fat milk (select all that apply)?
    i. Better body composition
    ii. Healthier growth rate
    iii. Better brain development
    iv. Obesity prevention

v. Better nutrition (fat soluble vitamins etc.)
vi. Other (please specify)
vii. None

8. What do you think are the harms of providing children older than 2 years of age with reduced (1% or 2%) fat milk (select all that apply)?
   i. May cause higher adiposity
   ii. Higher saturated fat intake
   iii. Creation of higher fat dietary pattern
   iv. Other (please specify)
   v. None

Parents:

1. What cow's milk fat recommendation did your child's physician make during their 2-year well-child visit, if any?
   a. Skim (0.1%)
   b. 1%
   c. 2%
   d. Whole/homo (3.25%)
   e. None
2. What fat content of cow's milk do you usually provide to your child?
   a. Skim (0.1%)
   b. 1%
   c. 2%
   d. Whole/homo (3.25%)
3. Why do you choose this fat content of cow's milk for your child?
   a. Recommended by my child's physician
   b. Recommended by Canada's Food Guide, Health Canada or Canadian Pediatric Society (web or print)
   c. Recommended by friend/family
   d. Other (please specify)
4. What do you think are the benefits of providing children older than 2 years of age with whole (3.25% fat) milk (select all that apply)?
   i. Better body composition
   ii. Healthier growth rate
   iii. Better brain development
   iv. Obesity prevention
   v. Better nutrition (fat soluble vitamins etc.)
   vi. Other (please specify)
   vii. None
5. What do you think are the harms of providing children older than 2 years of age with whole (3.25%) fat milk (select all that apply)?
   i. May cause higher adiposity
   ii. Higher saturated fat intake
   iii. Creation of higher fat dietary pattern
   iv. Other (please specify)
   v. None
6. What do you think are the benefits of providing children older than 2 years of age with reduced (1% or 2%) fat milk (select all that apply)?
   i. Better body composition

ii. Healthier growth rate
iii. Better brain development
iv. Obesity prevention
v. Better nutrition (fat soluble vitamins etc.)
vi. Other (please specify)
vii. None

7. What do you think are the harms of providing children older than 2 years of age with reduced (1% or 2%) fat milk (select all that apply)?
    i. May cause higher adiposity
    ii. Higher saturated fat intake
    iii. Creation of higher fat dietary pattern
    iv. Other (please specify)
    v. None

Interview Script

Your participation in this questionnaire is voluntary. You may refuse to take part in the research or stop the interview at any time without penalty. You are free to decline to answer any particular question you do not wish to answer for any reason. The decision to participate or not, and the responses given, will have no impact on your [physicians: position or evaluation; parents: access to customary care at] at St. Michael's Hospital. You will receive no direct benefits from participating in this research study. Your responses will help us learn more about your attitudes towards cow's milk fat and help us to develop a new clinical trial tailored to your needs. There are no foreseeable risks involved in participating in this study other than those encountered in day-to-day life and potential inconvenience of 15 minutes of your time. Your answers will be kept confidential and will not be traceable to you. The results of this study may be presented at a scientific conference or published in a scientific journal. We expect that the results of the study will be available in 1 year. Direct quotes may be used in publications. All audiotape recordings will be transcribed word for word (except for any identifying information, which will not be transcribed). Recordings will be destroyed once the transcribed information has been assessed for accuracy. The audio tape recordings and the transcripts will be assigned identification numbers, and will not be labeled with your name or other identifiers. The transcripts will be stored with and destroyed at the same time as the other study data.

Physicians:

1. Have you ever wondered what is the best fat content of cow's milk for children?
2. What are the current clinical guidelines for milk fat consumption among children over age 2?
3. How do you feel about these guidelines?
    i. Do you think these guidelines are beneficial? Why?
    ii. Do you think these guidelines are detrimental? Why?
4. Can you tell me about the last time you provided a milk fat recommendation for a child's diet?
    i. How did the child's parent(s) react?
    ii. Was this a typical reaction?
    iii. How often do you make cow's milk fat recommendations?
    iv. Can you remember any specific moment about recommending milk fat to parents?
        1. If not- Do they always agree?

5. Would you ever recommend the average child over age 2 to consume whole (3.25% fat) cow's milk? (yes/no) Why or why not?
6. If you were to recommend whole milk to a child over age 2 years, do you anticipate any barriers to doing so? What would facilitate this?

Parents:

a. How many children do you have?
b. What is your age range?
   i. Under 29
   ii. 30-39
   iii. Over 40
c. Can you tell me about the last time you needed nutrition advice/information for your child? (If necessary: What were you looking for? Where did you find it?)
d. What do you think about fat in your child's diet?
e. What do you think about cow's milk in your child's diet?
f. Have you ever wondered what fat content of cow's milk is best for your child? Tell me more about that. When?
g. What fat content of cow's milk (i.e. skim, 1%, 2%, whole (3.25%)) do you (or in the past, have you) provide your child? Why?
h. For parents of children who drink reduced fat milk: If your child's physician recommended a higher fat content for your child to consume, would you follow this recommendation? (yes/no) Why or why not?
i. For parents of children who drink whole fat milk: If your child's physician recommended your child to continue drinking whole milk beyond age 2, would you follow this recommendation? (yes/no) Why or why not?
j. What are your thoughts when you hear "skim milk" or "whole milk?"
k. Is there a situation when you would never provide whole (3.25%) cow's milk to your child?
l. Is there a situation when you would never provide reduced fat (skim, 1% or 2%) cow's milk to your child?
m. What would make it easier for you to provide whole cow's milk to your child when they are older than 2 years of age if you were asked to do so?

8.4 Supplementary Material for Cow's Milk Fat Obesity pRevention Trial (CoMFORT): A primary care embedded randomized controlled trial to determine the effect of cow's milk fat on child adiposity

REB Approval Letters

UNITY HEALTH TORONTO | PROVIDENCE Healthcare | ST JOSEPH'S HEALTH CENTRE TORONTO | St. Michael's Inspired Care. Inspiring Science.

Research Ethics Office
Telephone: (416) 864-6060 Ext. 2557
Facsimile: (416) 864-6043
E-mail: pateld@smh.ca

March 07, 2019

Dr. Jonathon Maguire,
St. Michael's Hospital

Dear Dr. Maguire,

Re: REB# 18-369 - Cow Milk Obesity pRevention Trial: CoMFORT

REB APPROVAL:	**Conditional Approval Date**	**March 7, 2019**

The above referenced study was received by the Unity Health Toronto Research Ethics Board (REB) on **November 29, 2019** for review.

This letter does not constitute approval by the REB for the commencement of this research study.

Final unconditional REB approval for this study will only be granted following the resolution of outstanding issues brought forward during the review.

The REB permits the use of this letter only:

1) For the purposes of/or to receive disbursement from Unity Health Toronto. No research involving humans can proceed without REB approval.

Unity Health Toronto Research Ethics Board (REB) operates in compliance with the Tri-Council Policy Statement Ethical Conduct for Research Involving Humans, the Ontario Personal Health Information Protection Act, 2004, and ICH Good Clinical Practice Consolidated Guideline E6, Health Canada Part C Division 5 of the Food and Drug Regulations, Part 4 of the Natural Health Product Regulations, and the Medical Devices regulations. Furthermore, all investigational drug trials at Unity Health Toronto REB are conducted by Qualified Investigators (as defined in the latter document).

With best wishes

☐ David Mazer, MD
Chair, Research Ethics Board

☐ Philip Berger, MD
Vice Chair, Research Ethics Board

☐ Michael Heffer, BSc.Phm. MHSc.
Vice Chair, Research Ethics Board

☐ Michael Szego, PhD
Vice Chair, Research Ethics Board

DM/PB/MS/MH/JL

Dr. Jonathon Maguire (REB# 18-369) Template V.2 Page 1 of 1

Research Ethics Office
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UNITY HEALTH TORONTO

January 28, 2020

Dr. Jonathon Maguire,
Department of Paediatrics,
St. Michael's Hospital

Dear Dr. Maguire,

Re: REB# 18-369 - Cow Milk Obesity pRevention Trial: CoMFORT

REB APPROVAL:	**Original Approval Date**	**October 23, 2019**
	Annual/Interval Review Date	**October 23, 2020**

Thank you for your communications dated **October 29, 2019** regarding the above named study.

The submission has been reviewed and the Unity Health Toronto Research Ethics Board (REB) hereby issues approval for:

1. Parental Consent ver: 1 10/25/2019
2. Protocol ver: 1.1 10/25/2019

Please note that no member of the REB associated with this submission was involved in its deliberation, review or approval.

During the course of this investigation, any significant deviations from the approved protocol and/or unanticipated developments or significant adverse events should immediately be brought to the attention of the REB. Furthermore, it should be acknowledged that shared electronic health systems such as ConnectingOntario, PRO, RM&R, OLIS, HDIRS, eCHN, DPV, and IAR do not permit access for research purposes. *For studies which are registered on a publicly available Clinical Trials registry (e.g. ClinicalTrials.gov), please ensure the record is updated to accurately reflect the status of the study.*

The REB operates in compliance with the Tri-Council Policy Statement Ethical Conduct for Research Involving Humans, the Ontario Personal Health Information Protection Act, 2004, and ICH Good Clinical Practice Consolidated Guideline E6, Health Canada Part C Division 5 of the Food and Drug Regulations, Part 4 of the Natural Health Product Regulations, and the Medical Devices regulations. Furthermore, all investigational drug trials at Unity Health Toronto are conducted by Qualified Investigators (as defined in the latter document).

With best wishes

☑ David Mazer, MD, Chair, REB
☐ Michael Szego, PhD, Vice Chair, REB
☐ Philip Berger, MD, Vice Chair, REB
☐ Zoe von Aesch, MD, Vice Chair, REB

DM/PB/MS/ZVA/JL

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UNITY HEALTH TORONTO

October 23, 2019

Dr. Jonathon Maguire,
Department of Paediatrics,
St. Michael's Hospital

Dear Dr. Maguire,

Re: REB# 18-369 - Cow Milk Obesity pRevention Trial: CoMFORT

REB APPROVAL:	**Original Approval Date**	**October 23, 2019**
	Annual/Interval Review Date	**October 23, 2019**

Thank you for your application submitted on **November 29, 2018**. At the Unity Health Toronto Research Ethics Board (REB) meeting held on December 12, 2018, the above referenced study was discussed and subsequently the views derived from this discussion have been documented and resolved. Please note that no member of the REB associated with this study was present or involved in its deliberation, review or approval.

The REB approves the study as it is found to comply with relevant research ethics guidelines, as well as the Ontario Personal Health Information Protection Act (PHIPA), 2004. The REB hereby issues approval for the above named study for a period of 12 months from the date of this letter. Continuation beyond that date will require further review of REB approval.

The REB has only granted approval of this study for the following sites under the auspices of Unity Health Toronto: 61 Queen Street, 80 Bond Street, 410 Sherbourne Street, 73 Regent Park Blvd.

In addition, the following are appropriate and hereby approved:

1. Protocol ver: 1 9/23/2019
2. Consent Form - Physician Consent ver: 1 9/6/2019
3. Consent Form - Parental Consent ver: 1 10/21/2019
4. ASA24 Diet Survey Information ver: 1/1/2018
5. RA Troubleshooting Guide ver: 1 9/6/2019
6. RA Follow up Phone Call Script ver: 1 9/6/2019
7. Physician Reminder Poster ver: 9/6/2019
8. Magnet: 1% Milk is Healthy ver: 1.3 9/30/2019
9. Magnet: 3.25% Milk is Healthy ver: 1.3 9/30/2019
10. Study Information for Parents - 1% milk fat ver: 1 9/6/2019
11. Study Informaiton for Parents - 3.25% milk fat ver: 1 9/6/2019
12. TARGet Kids Re-Consenting Script/already enrolled in COMFORT ver: 1 9/6/2019

Furthermore, the following documents have been received and are acknowledged:

1. CoMFORT Follow Up Email Survey Script ver: 1 9/6/2019
2. ASQ-3: 18 Month, 24 month, 48 month ver: 2009
3. Screening Eligibility Form ver: 5/30/2019
4. Early Development Instrument ver: 2000
5. Follow up Email Survey and Phone Call Data Sheet ver: 9/6/2019

During the course of this investigation, any significant deviations from the approved protocol and/or unanticipated developments or significant adverse events should immediately be brought to the

Consent Form

St. Michael's
Inspired Care.
Inspiring Science.

TARGet Kids!
Cow Milk Fat Obesity pRevention Trial *(CoMFORT)* Study

SickKids
THE HOSPITAL FOR SICK CHILDREN

Why am I being asked to take part in this research?
Your child is a part of *TARGet Kids!* and this is a study for which you are eligible to participate. The *TARGet Kids!* Research group hopes to learn more about how we can provide the best care to keep children healthy as they grow and develop, including recommending the best type of milk for children.

The *TARGet Kids!* CoMFORT Study aims to find out which type of cow's milk is best for children. Whole (3.25%) and reduced fat (1%) cow's milk are widely available and consumed by many Canadian children. The purpose of this study is to find which milk recommendation lessens the risk of obesity in children and optimizes child nutrition and development.

We are inviting you to help us try and answer this question.

What do I need to do?
Children who participate in this study will be randomly assigned (have an equal chance like the flip of a coin) to receive whole (3.25%) or reduced (1%) fat milk for your child. This selection is done by the study team. Your child's doctor will let you know which cow's milk fat your child should drink based on this random assignment. We will be using information already collected as part of the *TARGet Kids!* study to help determine which milk is best, and will be conducting bi-monthly email surveys or phone calls for the study duration (until your child is 4 years old) to see how things are going.

Will I receive any compensation for participating in the study?
We will provide you with a $25 grocery store gift card for your participation.

What would happen if I weren't in the study?
You would receive usual care from your physician.

What are the Risk and Benefits?
Since whole and reduced fat milk recommendations are currently part of usual healthcare, the risks to your child in participating are no greater than in usual care. There is no expected direct benefit to you.

health research for every child TARGetKids!

Important information

- Participation is voluntary
- You can withdraw consent at any time by talking to the *TARGet Kids!* research assistant
- Your data will be de-identified and confidentially maintained as discussed in the *TARGet Kids!* consent form
- To ensure proper study conduct, members of Sick Kids or Unity Health Toronto Research Ethics Board may review your study related data

Questions?

- If you have any questions about your participation you can contact the TARGet Kids! Research Manager: Dalah Mason or Principal Investigator: Jonathon Maguire @ 416-813-7654 ext. 302129.
- If you have any questions about your rights as a research participant or the conduct of this study, you may contact the Unity Health Toronto Research Ethics Board: 416-864-6060 ext. 2557 or the Sick Kids Research Ethics Board at 416-813-8279.

By signing this research consent form, I understand and confirm that:

1. All of my questions have been answered,
2. I understand the information within this informed consent form,
3. I understand that no information about my child will be given to anyone or be published without my permission.
4. I do not give up any of my or my child's legal rights by signing this consent form,
5. I have been told that I will be given a signed and dated copy of this consent form.
6. I agree to allow the child for whom I am responsible, to take part in this study.

I agree, or consent that my child ____________________________ may take part in this study.

______________________________ ______________________________

Printed Name of Parent/Guardian | Parent/Guardian signature & date (DD/MMM/YYYY)

______________________ _______________ ______________________

Printed Name of person who obtained consent | Role of person obtaining consent | Signature & date (DD/MMM/YYYY)

Intervention Scripts for Physicians

Reduced (1%) fat milk:

"Your child is recommended to consume 2 cups or 500 mL of 1% cow's milk each day. Do you have any questions about that?"

Whole (3.25%) fat milk:

"Your child is recommended to consume 2 cups or 500 mL of whole or 3.25% cow's milk each day. Do you have any questions about that?"

Reminder Magnets

Reminder Email Script

Your child is part of the TARGet Kids! CoMFORT study about cow's milk. We would like you to answer 3 short questions about cow's milk in your child's diet.

1. At your child's most recent well-child visit, what milk fat content recommendation did your child's physician provide?
    a. Skim (0.1%)
    b. 1%
    c. 2%
    d. Whole (3.25%)
2. What fat content of milk has your child been drinking for the past month?
    a. Skim (0.1%)
    b. 1%
    c. 2%
    d. Whole (3.25%)
3. Please select the most applicable reason for your choice to provide that fat content of cow's milk to your child:
    a. Physician recommendation
    b. Daycare/care provider serves it
    c. Family/friend suggestion
    d. Sibling/other family member drinks it
    e. Other: ____________

For children randomized to the whole milk intervention,

Please remember to provide whole (3.25%) milk cow's milk to your child.
Two cups (500 mL) is recommended each day.

For children randomized to the reduced fat milk intervention,

Please remember to provide 1% milk cow's milk to your child.
Two cups (500 mL) is recommended each day.

CHAPTER 9: REFERENCES

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