AGE OF COW MILK INTRODUCTION
AND CHILDHOOD GROWTH

By

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Department of Nutritional Sciences
University of Toronto

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ABSTRACT

Recommendations on the age that children can start consuming cow milk vary between countries. In Canada and Denmark, cow milk can be introduced as early as 9 months; however, in most countries it is recommended to wait until 12 months. Through this thesis I aimed to determine if the age that cow milk is first introduced into the diet influences childhood growth. In this prospective study of healthy children enrolled in the TARGet Kids! cohort, introducing cow milk at a younger age was associated with greater height by age 3-5 years. Each month earlier that cow milk was introduced was associated with 0.03 higher height-for-age z score or 0.1 cm per month. There was no significant association between timing of cow milk introduction and adiposity. In this cohort of children aged 3-5 years starting to consume cow milk earlier in life contributed to gains in height, without adversely affecting adiposity.
AKNOWLEDGMENTS

Completing my master’s has been a humbling experience. I feel extremely grateful for the opportunity to have worked with, and to continue working with, the TARGet Kids! research team. First and foremost, I would like to sincerely thank my supervisor, Dr. Jonathon Maguire, for his selfless support, encouragement and patience. It has been a privilege to work with someone as knowledgeable, inspiring and open-minded.

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Finally, I must thank my best friend, Kearney Nugent, who has experienced all of the ups and downs of my research with me. Thank you for continuously and selflessly supporting my education, but more importantly for always believing in me and encouraging me to follow my dreams.

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<tbody>
<tr>
<td>AAP</td>
<td>American Academy of Pediatrics</td>
</tr>
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<td>BMI</td>
<td>Body Mass Index</td>
</tr>
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<td>CCHS</td>
<td>Canadian Community Health Survey</td>
</tr>
<tr>
<td>CDC</td>
<td>Centers for Disease Control and Prevention</td>
</tr>
<tr>
<td>CPS</td>
<td>Canadian Paediatric Society</td>
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<tr>
<td>CI</td>
<td>Confidence interval</td>
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<tr>
<td>DRI</td>
<td>Dietary Reference Intakes</td>
</tr>
<tr>
<td>EAR</td>
<td>Estimated Average Requirement</td>
</tr>
<tr>
<td>GI</td>
<td>Gastrointestinal tract</td>
</tr>
<tr>
<td>IGF-1</td>
<td>Insulin-growth-like factor-1</td>
</tr>
<tr>
<td>IOM</td>
<td>Institute of Medicine</td>
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<td>IU</td>
<td>International Unit</td>
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<td>mg</td>
<td>milligrams</td>
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<td>milliliters</td>
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<td>NHANES</td>
<td>National Health and Nutrition Examination Survey</td>
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<td>RDA</td>
<td>Recommended Dietary Allowance</td>
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<td>SD</td>
<td>Standard Deviation</td>
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<td>WHO</td>
<td>World Health Organization</td>
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STUDENT CONTRIBUTIONS

- Conceptualized research question and study design
- Cleaned data
- Designed the analytical plan
- Conducted statistical analysis using the R program
- Presented research findings at the 2018 Pediatric Academic Societies Conference in Toronto, Ontario
- Presented research findings at the St Michael’s Hospital Research Trainee Day placing first in the poster competition.
- Drafted and revised the manuscript
CHAPTER 1: INTRODUCTION

Nutrition is an important determinant of growth in early childhood [1]. Cow milk is a convenient and widely accessible source of nutrients in young children’s diet [2, 3]. Most countries recommend that young children consume cow milk daily to support growth [2, 3]. However, recommendations on the age that cow milk can become part of the child’s diet vary between countries [4, 5]. The age that cow milk is first introduced into the diet may influence growth in later childhood. Regular consumption of cow milk during childhood has been associated with increased height [6-9], suggesting that starting to consume cow milk earlier in life may contribute to gains in height. However, greater milk intake has also been associated with more rapid weight gain [10], suggesting that delaying the introduction of cow milk may lower a child’s future risk of obesity.

Surprisingly little is known about the relationship between timing of cow milk introduction and childhood growth. In many countries, such as the United States, cow milk is not recommended for children younger than one year of age; therefore, few studies have been able to examine this relationship [11]. Canada is one of the few countries where cow milk may be introduced as early as 9 months of age [5], providing a unique opportunity to examine differences in growth among children who start consuming cow milk during the first year of life.

The primary objective of this thesis was to evaluate the association between the age of cow milk introduction and height at 3 to 5 years of age. Secondary objectives were to examine the association between the age of cow milk introduction and the volume of cow milk consumed and adiposity at age 3 to 5 years.
The thesis is organized into 7 chapters. The following literature review (Chapter 2) is divided into 3 sections: (1) childhood growth (2) cow milk consumption in children and (3) cow milk consumption and childhood growth, with a focus on height and weight. The potential mechanisms by which cow milk may contribute to height and adiposity in children will also be discussed. Chapter 3 includes the research study titled ‘Age of cow milk introduction and childhood growth’. Chapter 4 is an overall discussion, and Chapter 5 provides concluding statements and future directions for this research. Lastly, Chapter 6 lists the references and Chapter 7 the appendices.
CHAPTER 2: LITERATURE REVIEW

Section 1: Childhood growth

1.1. Early growth and nutrition

Childhood growth has been associated with health in later life [1, 12]. For example, failure to achieve one’s genetic potential for height has been associated with poor cognitive function, lower school achievement and an increased risk of disease later in life [12-14]. At the other end of the spectrum, rapid growth in early life has been associated with later obesity [10, 15]. Overweight children are more likely to become overweight adults, placing them at increased risk of cardiovascular disease, hypertension and diabetes [16].

Nutrition is an important determinant of growth, especially during the first few years of life [17]. Adequate nutrition is necessary to sustain children’s rapid rate of growth and to ensure that children grow and develop to their full potential [18]. Growth during childhood is therefore a useful tool to gauge children’s nutritional status and deviations from growth may be indicative of suboptimal nutrition [12]. For example, poor growth may indicate undernutrition (nutrient intake below daily requirements), whereas, rapid growth may suggest overnutrition (nutrient intake above daily requirements) [19]. Early dietary factors that promote optimal growth by minimizing the risk of undernutrition and overnutrition can help maximize children’s future health.

1.2. Growth assessment

Monitoring growth is an efficient way to assess nutritional status in children and is recommended to be performed at each primary care visit [12, 20]. Childhood growth has been widely and successfully assessed by using anthropometric measures [21]. The most commonly used
anthropometric measurements are weight and height as they are rapid, cost-effective and easy to obtain [22].

Standardized methods for measuring children’s height and weight are recommended to be used to ensure accurate and precise measurements [22, 23]. For children 2 years and older, the Canadian Paediatric Society and Dietitians of Canada recommend that weight be measured using a precision digital scale and standing height be measured without shoes using a calibrated stadiometer. For children less than 2 year of age, it is recommended that a calibrated length board be used to measure recumbent length [21, 24].

1.3. Adiposity measurement

There are various ways to measure adiposity (body fat) in children. One method is dual-energy X-ray absorptiometry (DXA), which generates x-rays that pass through the subject to estimate the relative proportion of body fat and lean body mass [22, 25]. Other body composition measuring techniques include air displacement plethysmography (Bod Pod and Pea Pod) and bioelectrical impedance analyzers (BIA) [22]. Direct measures of adiposity are highly accurate and precise. However, their use in clinical practice is limited because they are expensive, potentially harmful and not practical. For example, DXA involves exposure to radiation, and the Bod Pod requires sitting in an expensive and large sealed chamber [22].

For practicality purposes, body mass index (BMI) is the internationally recommended indicator of adiposity in children [22, 23]. BMI is a measure of weight adjusted for height (BMI = kg/m^2) [24] and has been shown to correlate strongly with other direct measures of adiposity (e.g. DXA) and with future obesity risk [22, 23].
1.4. Growth standards

Assessment of growth and nutritional status in clinical settings requires comparing the child’s weight and height measurements with growth references of healthy children the same age and sex [26]. Widely used growth references include the United States 2000 Center for Disease Control and Prevention (CDC) growth references [27] and the Euro Growth references [28], which describe how children grew in the United States and Europe, respectively.

In 2006, the World Health Organization (WHO) released new child growth standards for infants and children up to the age of 5 years, which are considered the gold standard for assessing the growth of children 0-5 years of age in Canada [29]. These new growth standards were developed by following more than 8000 children from 6 different countries (Brazil, Ghana, India, Norway, Oman and the United States) raised under optimal conditions (e.g. non-smoking households, predominately breastfed) [30]. As such, the WHO growth standards aim to represent optimal growth and suggest a pattern of growth for all children to achieve. Since the WHO growth charts depict how children should grow under optimal conditions, they are called growth standards. Whereas, the CDC growth charts are called growth references because they describe how children actually grew over a specified period of time in the United States [29]. Since the WHO growth standards are based on children from different parts of the world they can be used for multiethnic populations in Canada [31]. The WHO growth standards for children 0-5 years of age can be found in Appendix A and B.

1.5. Interpretation of WHO growth charts

Once weight and height have been measured, the child’s growth and overall nutritional status can be assessed by calculating z score values for height and BMI using the 2006 WHO child growth
standards. A height-for-age and BMI $z$ score is an age and sex normalized measure of a child’s height and weight provided in units of standard deviations (SD) relative to the WHO reference population [31]. The $z$ score describes how far a child’s weight or height measurement is from the median or the 50th percentile. A positive (+) or negative (−) sign depends on whether the child’s height or weight is above or below the median height or weight of the WHO reference population for a child the same age and sex [21]. For example, a BMI $z$ score of 2 means the child’s weight is 2 SDs above the median. If the actual BMI of a child is exactly equal to the median in the WHO reference population, the BMI $z$ score would be equal to 0 (zero) [21]. The median or the 50th percentile is not meant to be the goal for every child [24]. All children grow differently, and some children have the genetic potential to be taller, shorter or heavier [12]. However, most children follow the same percentile curve over time and a sharp decline or incline, or a line that is flat, may indicate poor growth or excess weight gain [24].

1.6. Determinants of height

A person’s final attained height is influenced not only by genetics, but also by modifiable environmental factors during childhood [14]. It has been estimated that about 20% of the variance in height between individuals may be attributed to environmental factors [32]. An important modifiable factor of childhood height is nutrition [17]. Adequate nutrition in early life ensures that children reach their genetic height potential, defined as the maximum height an individual can grow under optimal conditions [14, 17, 33].

Other environmental factors believed to be associated with childhood height include food allergies, socioeconomic status, birth weight and illness. Food allergies that arise early in life may affect nutrition, which in turn can lead to poor growth [34, 35]. Similarly, socioeconomic
status (income, education, unemployment, financial hardship) are believed to be negatively associated with height because they represent access to resources, health care and are intertwined with nutrition and disease [14, 36]. Lastly, there is some evidence that birth weight is positively associated with later height. A recent study (2018) based on data from 28 twin pairs in 17 countries observed that a 1 kg increase in birth weight was associated with 1.14 to 4.25 cm greater height in adulthood [37].

Section 2: Cow milk consumption in children

2.1. Cow milk consumption in children

Cow milk is a dietary staple for the majority of children in North America [2, 3]. According to the results from the 2004 Canadian Community Health Survey (CCHS), approximately 88% of 1 to 3-year-old children consumed cow milk on a daily basis [3]. The Nutrition Committee of the Canadian Paediatric Society recommends cow milk as a source of nutrients important for growing children [5]. International guidelines, such as those from the American Academy of Pediatrics, also recommend daily cow milk consumption during childhood for proper growth and development [11, 38].

2.2. Macronutrients in cow milk

The Nutrition Facts table for whole (3.25% fat) cow milk is shown in Table 1. Cow milk is a source of macronutrients (carbohydrates, protein and fat) which help support the energy needs of growing children [39]. One cup (250 ml) of whole cow milk provides 12 grams of carbohydrates, 8 grams of fat and 9 grams of protein [40].
Table 1: Nutrition facts table for whole (3.25% fat) cow milk

Carbohydrates

The main carbohydrate in cow milk is a disaccharide called lactose (commonly referred to as ‘milk sugar’) which consists of the two monosaccharides glucose and galactose [41]. In the body, lactose is broken down into glucose and galactose by an enzyme called lactase [38, 42]. The carbohydrates in cow milk provide a readily available source of energy for the cells of the body which are most rapidly liberated in response to physical activity [41].

Fat

Fat is a concentrated source of energy, which is important during childhood when energy requirements are particularly high [43]. Fat also provides essential fatty acids important for brain development, helps with the absorption of fat-soluble vitamins (A, D, E and K), promotes satiety and enhances the flavour of foods, which can affect acceptability [44].
**Protein**

Protein fuels the growth of new cells and plays an important role in bone growth [41]. Protein needs are particularly high during childhood to allow for tissue growth [45]. Protein from animal sources, such as cow milk, are commonly referred to as ‘high quality’ or ‘complete proteins’ because they provide all of the nine essential amino acids [45]. Whereas, plant-based proteins (e.g. legumes, grains, nuts, seeds) are called ‘incomplete proteins’ because they are deficient in one or more of the nine essential amino acids (e.g. legumes are deficient in the amino acid methionine; cereal grains are deficient in the amino acid lysine) [45]. Children who only consume plant-based proteins are recommended to consume a varied diet containing complementary proteins to ensure adequate intake of the nine essential amino acids [45].

**2.3. Micronutrients in cow milk**

Cow milk is also a reliable source of micronutrients such as calcium and vitamin D, which can be challenging for young children to obtain from other sources [5, 39]. Calcium and vitamin D are nutrients essential for optimal growth and work together to promote bone health [41, 46-48].

**Vitamin D**

Vitamin D (also known as the ‘sunshine vitamin’) is a fat-soluble vitamin produced by the body when the skin is exposed to UV light [41]. “Exposure of arms and legs for 5 to 30 minutes (depending on the location, time of day, season and skin pigmentation) between the hours of 10 a.m. and 3 p.m. twice a week” is often adequate to produce sufficient amounts of vitamin D [48]. However, minimizing exposure to direct sunlight is recommended for children to reduce the risk of skin cancer. Further, during the 5-6 months of winter in Canada, solar UV radiation is not
strong enough to synthesize vitamin D [48]. For these reasons, it is recommended that children meet their daily vitamin D requirements through dietary sources.

*Vitamin D fortification of cow milk in Canada*

The Canadian Food and Drug Act mandates that all cow milk in Canada be fortified with 100 International Units (IU) of vitamin D per cup (250 ml), making it the main dietary source of vitamin D in children’s diets [39, 47, 49]. A joint statement released by Health Canada, the Canadian Paediatric Society, Dietitians of Canada and the Breastfeeding Committee for Canada recommends that non-breastfed children consume two cups (500 ml) of cow milk daily to help meet their daily vitamin D requirement [5].

*Calcium*

Cow milk provides a bioavailable source of calcium in young children’s diet [38]. Almost all of the calcium in the body is stored in bones and teeth and the remaining ~1% in the bloodstream [50]. Calcium is necessary for numerous intercellular processes, so blood calcium levels are tightly regulated through an endocrine feedback loop [47]. When blood calcium levels rise, parathyroid hormone (PTH) is secreted. PTH stimulates the activation of vitamin D through hydroxylation to its active form (1-25-hydroxyvitamin D) in the kidneys and liver. The activation of vitamin D causes the kidneys to reabsorb more calcium, increases the absorption of calcium in the small intestine and causes osteoclasts (bone cells) to break down bone, releasing calcium into the bloodstream. Through these three mechanisms, blood calcium levels rise. Ensuring adequate intake of calcium from the diet helps to keep calcium in the bone [41, 50] (see: **Figure 1**: Regulation of blood calcium levels).
Dietary reference intakes

Dietary reference intakes (DRIs) are recommendations for nutrient intakes established by the Institute of Medicine (IOM). The DRIs for vitamin D and calcium are based on dietary requirements for optimal bone health and include the Estimated Energy Requirement (EAR) and the Recommended Dietary Allowance (RDA) [50]. The EAR is defined as the level of intake that would meet the requirements of half of the population (i.e. the median intake). The RDA is the level of intake that would meet the requirements of at least 97.5% of the population, set as two SD above the EAR [50].
DRIs for vitamin D

The RDA for vitamin D for children 1 to 8 years of age is 600 IU per day. Few foods naturally contain vitamin D. The primary sources of vitamin D in the diet include fortified foods (e.g. cow milk, margarine), egg yolk and fatty fish such as salmon and trout [40]. Two cups of cow milk provide 200 IU of vitamin D, which meets about 30% of the daily vitamin D requirement for a child 1-8 years of age [40, 50] (see Table 2: Vitamin D requirements for young children).

Table 2: Vitamin D requirements for young children

<table>
<thead>
<tr>
<th>Life-stage group</th>
<th>EAR (intake that covers 50% of the population)</th>
<th>RDA (intake that covers ≥ 97.5% of the population)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Children</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 – 3 years</td>
<td>400 IU</td>
<td>600 IU</td>
</tr>
<tr>
<td>4 – 8 years</td>
<td>400 IU</td>
<td>600 IU</td>
</tr>
</tbody>
</table>

DRIs for calcium

The RDA for calcium for children 1-3 years of age is 700 milligrams (mg) per day. Major food sources of calcium include dairy products (e.g. cow milk, yogurt, cheese), leafy green vegetables (e.g. kale, collard greens), tofu, molasses, legumes (e.g. beans), nuts and seeds (e.g. sesame seeds, almonds) [47]. A daily intake of 2 cups of cow milk largely satisfies the calcium requirements of children 1-3 years of age. For example, two cups of cow milk provide 580 mg of calcium, which meets about 80% of the daily requirement of children of this age group (see Table 3: Calcium requirements for young children).
Table 3: Calcium requirements for young children

<table>
<thead>
<tr>
<th>Life-stage group</th>
<th>EAR (intake that covers 50% of the population)</th>
<th>RDA (intake that covers ≥ 97.5% of the population)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Children</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 – 3 years</td>
<td>500 mg</td>
<td>700 mg</td>
</tr>
<tr>
<td>4 – 8 years</td>
<td>800 mg</td>
<td>1000 mg</td>
</tr>
</tbody>
</table>

2.4. Standardization and regulation of cow milk in Canada

Although the addition of vitamin D to cow milk is tightly regulated, a Canadian study observed a wide variation in the vitamin content of Ontario retail milk. The study found that only 20% of whole cow milk samples contained the recommended amount of vitamin D. The majority of the samples were overfortified, while 27% of the samples were below the recommended level [49]. The authors concluded that the low levels of vitamin D in cow milk sold in Canada are a concern for young children and that more rigorous monitoring programs are needed.

2.5. Recommendations for the age of cow milk introduction

Most countries recommend that cow milk consumption be delayed until 9 or 12 months of age to reduce the risk of iron deficiency [5, 51]. In addition to being a poor source of iron, cow milk is known to inhibit the absorption of iron and may displace other iron-rich foods in the diet [52]. Previous studies have identified early consumption of cow milk as a major risk factor for iron deficiency in children [52, 53].

Variance in recommendations

Professional recommendations on the age that cow milk can first be introduced into the diet vary between countries. Infant feeding guidelines from Health Canada, Canadian Paediatric Society,
Dietitians of Canada and the Breastfeeding Committee for Canada suggest that cow milk may be introduced as early as 9-12 months of age once the older infant is consuming a wide variety of iron-rich foods, which is consistent with recommendations from the Danish Health Authority and the WHO [5, 51]. This is in contrast to recommendations from the United States, Australia and the United Kingdom which advise parents to wait until the child is at least one year of age before offering cow milk as a drink [51] (see Figure 3: International recommendations for the age of cow milk introduction).

![Figure 3: International recommendations for the age of cow milk introduction](image)

**Figure 2: International recommendations for the age of cow milk introduction**

*Adherence to recommendations*

Despite American recommendations to wait until 12 months of age before introducing cow milk into children’s diet, results from the 1999-2002 National Health and Nutrition Examination Survey (NHANES) found that 25% of parents reported that their child consumed cow milk on a daily basis before one year of age [8].

**2.6. Recommendations on milk fat**

Once cow milk is introduced into the child’s diet, Canadian guidelines recommend that only whole (3.25% fat) cow milk be consumed until 2 years of age [5]. Reduced-fat cow milk is not
recommended during the first two years of life because young children need the additional fat and energy in whole cow milk for normal growth and brain development [44].

2.7. Recommendations on milk intake

Once introduced, cow milk is recommended to be limited to 2-3 cups per day [5]. Limiting cow milk to less than 3 cups per day is recommended because too much cow milk in a child’s diet can increase the risk of iron deficiency, promote excess weight gain and displace other foods in the diet that contain nutrients not found in cow milk [43, 52, 53]. Research from our group has shown that for most children two cups of cow milk daily maintains healthy vitamin D stores, without negatively affecting iron stores [53].

2.8. Cow milk avoidance

Lactose intolerance

Some children may not be able to consume cow milk due to an intolerance or allergy to cow milk. Cow milk intolerance can be attributed to either the lactose or protein present in milk [54]. Lactose intolerance is the inability to digest lactose (the sugar in cow milk) because the body does not produce enough of the enzyme lactase [41]. If lactose is not broken down by the body, it remains in the intestine and can cause gastrointestinal tract (GI) symptoms such as gas, bloating, diarrhea and discomfort [54]. Lactose intolerance is more common among non-Caucasian populations (e.g. Asians, Africans, Native Americans and Hispanics). It has been estimated that approximately 20% of Hispanic, Asian and Black children younger than 5 years of age are lactose intolerant. Whereas, Caucasian children typically do not develop lactose intolerance until after 4-5 years of age [54].
Cow milk protein intolerance is a reaction to the protein (as opposed to the lactose) in milk. Symptoms are similar to those of lactose intolerance and may include vomiting, abdominal pain, blood in the stools and diarrhea [54].

Cow milk allergy

Cow milk allergy is an immune reaction to the proteins in milk that can be potentially fatal [41, 55]. In addition to GI symptoms, children with an allergy to cow milk may experience skin reactions (e.g. rashes, hives), respiratory symptoms (e.g. a runny nose, watery eyes) and, in severe cases, anaphylactic shock can occur [41, 55]. Cow milk allergy is the most common food allergy among young children affecting about 2-3% of children during the first year of life and then decreases with age [38, 56]. Treatment involves eliminating cow milk from the diet. Most children, however, outgrew their allergy and can tolerate milk by the age of 3 years [11, 55]. For example, in one study that prospectively followed 1749 Danish children from birth through 3 years of age, 87% of the children who developed an allergy to milk during the first year of life were able to tolerate milk by 3 years of age [55].

2.9. Replacement of cow milk with plant-based beverages

The replacement of cow milk with plant-based beverages, such as almond, oat, rice and coconut ‘milk’ is becoming more common, however, this dietary practice is poorly supported by evidence with unknown benefits or harms for young children [38]. Plant-based beverages (whether or not they are fortified) are not appropriate alternatives to cow milk during the first two years of life according to the Canadian Paediatric Society and Dietitians of Canada [5, 38]. With the exception of soy and pea protein ‘milks’, most plant-based beverages (e.g. almond, oat
and rice ‘milk’) are low in energy, fat and protein, which is a concern for growing children with increased nutritional requirements [5, 38]. In one study, consumption of rice milk was associated with an increased risk of malnutrition in children 1 to 2 years of age with atopic dermatitis [57].

Section 3: Cow milk intake and childhood growth

3.1. Cow milk consumption and childhood height

Evidence from observational [6-8] and intervention studies [9] suggest that cow milk contributes to growth in height in children. For example, a 2012 meta-analysis of intervention studies from around the world (Europe, United States, China, Vietnam, Kenya, Indonesia and India) identified that children 3 to 13 years of age who consumed an additional 245 ml of cow milk daily grew 0.4 cm the following year [9]. Evidence from the available studies focused specifically on young children (<5 years of age) also support cow milk’s role in promoting linear growth [6-8]. DeBoer et al., using data from a large cohort of 8950 children from the United States, observed that children who consumed greater amounts of cow milk at 4 years of age were taller, and remained taller when measured one year later. At 4 years of age, the difference between children who consumed ≥ 4 versus < 1 milk serving daily was a height-for-age z score of 0.2, corresponding to a difference of approximately 1 cm in height [6]. Similarly, in a study using data from NHANES 1999-2002, milk intake was a predictor of height in children at 2 to 5 years of age, even after adjusting for other factors that may influence childhood height such as ethnicity, birth weight, energy, protein and calcium intake. Children who drank cow milk daily were 1.01 cm taller compared to children who did not, which is similar to the 1 cm height difference observed in the study by DeBoer and colleagues.
3.2. Components of cow milk that potentially contribute to height

Many components of cow milk have been hypothesized to contribute to childhood height. Possible components are energy, protein, calcium, insulin-like growth-factor-1 (IGF-1) or a combination of these (see: Figure 3: Components in cow milk that may contribute to height).

Energy and protein

Since cow milk is a major source of dietary energy and protein in young children’s diet, some researchers have hypothesized that increased protein, or simply an overall increase in caloric intake, may contribute to height in children [58]. However, the evidence for this hypothesis is not well supported. For example, studies show that cow milk stimulates linear growth not only in developing countries with high rates of malnutrition [51, 58], but also in developed countries where energy and protein intake is generally adequate [6-8]. Further, Wiley (2009) has shown that adjusting for energy and protein intake does not attenuate the association between milk intake and height [8]. Lastly, higher protein intake did not appear to affect growth in an intervention study of 9-month-old infants from Denmark [59]. In this study, 83 healthy infants were randomized to receive either whole cow milk or infant formula from 9 to 12 months of age. Since cow milk contains almost twice as much protein as infant formula, the researchers hypothesized that the increased protein intake from cow milk would affect growth. Contrary to the hypothesis, no differences in growth were observed between infants given cow milk versus infant formula at one year of age. The researchers did, however, find that boys randomized to consume cow milk from 9-12 months had higher circulating levels of IGF-1 [59]. It is possible that any lack of difference between groups may have been due to insufficient study duration, as the trial was relatively short (3 months). The authors concluded that there is a need for future
studies examining the long-term effects of consuming cow milk during the period from 9 to 12 months of age.

![Diagram of Potential components: Calories, Protein, Minerals (e.g. calcium), Vitamins (e.g. vitamin D), Other components? to Cow milk, Growth, IGF-1]

**Figure 3:** Components in cow milk that may contribute to height. Modified from Hoppe et al. [58]

*Calcium*

Since calcium is important for bone growth, some researchers hypothesize that the calcium in cow milk may promote growth in children [60]. In the cross-sectional study of children 2-5 years of age by Wiley (2009) described earlier, adjusting for calcium intake attenuated the magnitude of the association between milk intake and height, suggesting that calcium may play, at least some role, in promoting linear growth [8]. However, the association between milk intake and height remained statistically significant after controlling for dietary calcium intake, indicating that there may be a component unique to cow milk that contributes to height, that is independent of calcium intake.

*IGF-1*

Since the association between cow milk intake and height appears to be independent of energy, protein and calcium intake, there may be unique properties of cow milk, such as IGF-1, that contribute to height. IGF-1 naturally present in cow milk is a hormone that is essential for normal growth in children [58]. Studies in children show that serum IGF-1 levels rise following
cow milk consumption [7, 59]. For example, in an observational study of 90 well-nourished 2.5-year-old Danish children, an increase in milk intake from 200 to 600 ml per day corresponded to a 30% increase in circulating levels of IGF-1, and higher IGF-1 levels were positively associated with height [7]. This suggests that IGF-1 levels are nutritionally regulated and thus may be modifiable, and that the effect cow milk on height might be, at least in part, mediated through IGF-1.

3.3. Cow milk avoidance and child height

Children who do not consume cow milk tend to be shorter [46, 61]. For example, Black et al. (2002) found that children aged 3 to 10 years from New Zealand (n = 50) with a long-history of cow milk avoidance had lower dietary calcium intakes and were significant shorter (0.65 z score units) compared to children who regularly consumed cow milk [46]. The authors concluded that nutritional inadequacies from cow milk avoidance may have contributed to shorter stature in children.

Similarly, a recent (2017) cross-sectional analysis of healthy Canadian children from our group identified that 3-year-old children who consumed 3 cups of non-cow milk beverages (e.g. almond, soy and rice ‘milk’) daily were, on average, 1.5 cm shorter compared to children who consumed similar amounts of cow milk daily [61]. The researchers speculated that children who consume milk alternative beverages might not receive adequate amounts of protein to support optimal growth. For example, the RDA for protein intake for a 3 year-old child is 13 grams per day [62]. Two cups of cow milk provide 16 grams of protein, which meets 100% of the daily protein requirement for a 3 year-old child [40]. Two cups of rice milk, on the other hand, only contains 1.4 grams of protein, which meets only 10% of the daily protein requirement [40].
3.4. Cow milk consumption and child adiposity

Research on cow milk consumption and adiposity in preschool children is limited and conflicting [6, 10, 63, 64]. Huh et al. (2010) examined the effect of cow milk intake on adiposity in a prospective cohort study of 852 preschool children from the United States. The results showed that milk intake at 2 years of age was associated with a slightly lower BMI z score (-0.09 unit per daily serving) at 3 years of age, but the association became null when restricted to children with a normal BMI at baseline [63]. In a large (n = 8950) prospective study also from the United states, consumption of higher amounts of cow milk (≥ 3 servings daily; above the recommended amount) was associated with a 0.1 higher BMI z score at 4 years of age. The association, however, was no longer significant at age 5 years leading the authors to conclude that the relationship between milk intake and adiposity may be weak, or age-dependent [6]. Lastly, in large prospective study of 12,829 American children 9 to 14 years of age, those who consumed more than 3 servings of cow milk daily gained more weight compared to children who consumed less than 1 serving [10]. However, adjusting for energy intake attenuated the association suggesting that the most important predictor of weight gain was total caloric intake, rather than cow milk consumption per se. This finding supports current recommendations for limiting cow milk intake to 2-3 cups per day to prevent unhealthy weight gain in children.

3.5. How cow milk may contribute to child adiposity

*Cow milk may add excess calories to the diet*

Energy requirements of a child are defined as the amount of energy needed to balance total energy expenditure and to support optimal growth [65]. Sustained positive energy balance (energy intake that exceeds energy requirements) can lead to excess weight gain in children.
Drinking large amounts of cow milk may promote child obesity by contributing excess calories to the diet [6, 10].

*The ‘early protein hypothesis’ and obesity risk*

The ‘early protein hypothesis’ suggests that a high protein intake (>15% of energy) early in life may increase the risk of obesity later in life [66]. It has been suggested that protein intake above requirements may stimulate IGF-1 production, which in turn may lead to an increase in the number and/or size of adipocytes (fat cells) [66]. The ‘early protein hypothesis’ was tested in a large randomized trial. Healthy formula-fed infants (n = 1138) from five European countries (Germany, Belgium, Italy, Poland and Spain) were randomized to consume either a lower or higher protein infant formula during the first year of life. The study found that at 2 years of age infants randomized to the higher infant formula gained more weight, suggesting that a lower protein intake early in life might diminish the risk of obesity later in life [67].

**3.6. Summary of literature review**

Achieving optimal growth in early life is important for maximizing children’s future health [12]. Cow milk provides energy, protein, calcium and other nutrients which are believed to support childhood growth [2, 3, 39, 58]. While most countries recommend cow milk consumption for young children, recommendations for the age that children can start consuming cow milk vary between countries [5, 51]. Children who regularly consume cow milk throughout childhood tend to be taller [6-9], suggesting that starting to consume cow milk earlier in life may positively influence child height. However, studies also suggest that cow milk intake has the potential to add excess calories to the diet and lead to weight gain, suggesting that delaying the introduction of cow milk may help to reduce a child’s future risk of obesity [10].
Considering that most young children in North American consume cow milk on a daily basis [3], and that timing of cow milk introduction may be modifiable, understanding this relationship has the potential to improve the health and nutrition of children in Canada. To the best of my knowledge, no studies have differences in growth from variations in the timing of cow milk introduction.
CHAPTER 3: AGE OF COW MILK INTRODUCTION AND CHILDHOOD GROWTH

1.1. Abstract

**Background:** International guidelines on the recommended age for children to start consuming cow milk vary between 9 and 12 months. The association between the timing of cow milk introduction and childhood growth is unknown.

**Objectives:** The primary objective was to evaluate the relationship between the age of cow milk and height at 3-5 years of age. Secondary objectives were to evaluate whether the timing of cow milk introduction was associated with volume of cow milk consumption or adiposity at 3-5 years of age.

**Design:** A prospective cohort study was conducted through the TARGet Kids! practice-based research network. Healthy children ≤ 2 years of age were recruited during a routine doctor’s visit between 2008 and 2016 and followed until 3 to 5 years of age. Data on age of cow milk introduction was collected at baseline using a parent-completed standardized questionnaire. The primary outcome was height-for-age z score at 3-5 years of age. Secondary outcomes were volume of cow milk consumed and BMI z score at 3-5 years of age. Multiple linear regression was used to examine the association between the age of cow milk introduction and childhood growth and volume of cow milk intake at 3-5 years of age.

**Results:** A total of 1903 children were included. On average, cow milk was introduced at 11.6 months. Most of the children (99.5%) had been introduced to cow milk by 2 years of age.
mean age at follow-up was 3.9 ± 0.6 years and the average length of follow-up was 2.5 years. In the primary analysis, earlier cow milk introduction was associated with greater height ($p < 0.001$). Each month earlier that cow milk was introduced was associated with 0.03 higher height-for-age $z$ score (95% CI: 0.05; 0.01) or 0.1 cm per month (95% CI: 0.11; 0.16 cm). At 4 years of age, the difference child introduced to cow milk at 9 months relative to 12 months was a height-for-age $z$ score of 0.1 (95% CI: 0.04; 0.16) or 0.4 cm in height (95 CI: 0.35; 0.47 cm).

Exploration for nonlinearity revealed the association between age of cow milk introduction and height was statistically significant after 9 months of age but not before. There was no statistically significant association between timing of cow milk introduction and volume of cow milk consumed ($p = 0.90$) or BMI $z$ score ($p = 0.20$) at follow-up.

**Conclusions:** Children who started to consume cow milk at a younger age appears to be taller by 3-5 years of age. Age of cow milk introduction was not associated with volume of cow milk consumed or child adiposity at 3-5 years of age. Future research is needed to understand the biological mechanisms and potential causality for the relationship between earlier milk intake and greater height.

### 1.2. Background

Growth monitoring is frequently used to assess children’s health and nutrition [24]. Promoting optimal growth is important for maximizing children’s health and developmental potential [13]. Nutrition is an important environmental factor affecting growth in early childhood [14]. Most countries recommend that young children consume cow milk daily to support growth [2, 3]. However, recommendations on the age that children can start consuming cow milk vary between countries. In Canada and Denmark, cow milk can be introduced as early as 9 months [5]. In the
United States, Australia and the United Kingdom, it is recommended to wait until one year of age before introducing cow milk [4].

Childhood growth may be sensitive to the age that cow milk is first introduced into the diet. Regular consumption of cow milk during childhood has been associated with increased height, suggesting that starting to consume cow milk at a younger age may contribute to gains in height [6, 68]. However, studies also suggest that greater cow milk intake may promote weight gain, suggesting that delaying the introduction of cow milk may help reduce the risk of child obesity [10, 15]. Since the timing of cow milk introduction is potentially modifiable understanding whether age of cow milk introduction influences growth in later childhood may provide an intervention target to maximize linear growth, while minimizing the risk of obesity in children. We hypothesized that a younger age of cow milk introduction would be associated with greater height, while an older age of cow milk introduction would be associated with lower adiposity.

The primary objective of the study was to evaluate the association between the age of cow milk introduction and height at 3 to 5 years of age among healthy Canadian children. Secondary objectives were to evaluate the association between the timing of cow milk introduction and volume of cow milk consumed and adiposity at 3 to 5 years of age.

1.3. Methods

Study design and population

A prospective cohort study was conducted through the TARGet Kids! practice-based research network in Toronto, Canada [69]. Between 2008 and 2016, healthy children ≤ 2 years of age
were recruited while attending a routine well-child visit from pediatric and family care practices located in the city and followed until 3 to 5 years of age.

Exclusion criteria

Children were excluded from the TARGet Kids! cohort if they had a known health condition which might affect feeding or growth (e.g. cerebral palsy), chronic illness (with the exception of asthma), severe developmental delay or born very preterm (before 32 weeks). For this study, children were further excluded if they did not consume cow milk by the follow-up visit. Written consent was obtained from all parents of participating children and the study was approved by the research ethics board at The Hospital for Sick Children and St. Michael’s Hospital.

Exposure and outcomes

Data was collected using a parent-completed standardized questionnaire adapted from the Canadian Community Health Survey [70] at the time of clinic visit. The primary exposure was age of cow milk introduction. To maximize recall, this was measured at the first TARGet Kids! visit following cow milk introduction (baseline visit) using the question: “At what age did you introduce cow milk?”

Physical measurements were obtained by trained research assistants at each clinic at the last TARGet Kids! visit prior to 5 years of age (follow-up visit). Standing height was measured without shoes using a calibrated stadiometer (SECA, Germany) and weight was measured using a precision digital scale (± 0.025%; SECA, Germany). The primary outcome was height-for-age z score. The secondary outcomes were volume of cow milk consumed and body mass index (BMI) z score. Daily volume of cow milk consumed was obtained from the following question:
“How many 250 ml cups of cow milk does your child drink in a typical day?” BMI (calculated as weight in kg/height in m²) is a widely used indirect adiposity measure that has been shown to correlate well with direct measures of adiposity [71-73]. Height-for-age and BMI were converted into z scores using the World Health Organization (WHO) child growth standards, which are believed to represent optimal growth in children [31, 74].

Potential confounders known or suspected to influence the association between the age of cow milk introduction and childhood growth were generated from a review of the literature. These included child age, sex, birth weight, maternal ethnicity, maternal height and BMI, self-reported household income, as well as total breastfeeding duration and daily sugar-sweetened beverage (SSB) consumption measured at the follow-up visit. Maternal ethnicity was categorized as European, Asian, African, Hispanic, Mixed and Other. Maternal BMI (measured at the follow-up visit) was calculated using the standard formula (kg/m²).

**Statistical Analysis**

Descriptive characteristics including means (± standard deviation) for continuous variables and counts and percentages for categorical variables were calculated to describe the study population. For the primary analysis, multiple linear regression was used to evaluate the relationship between the age of cow milk introduction and height-for-age z score at follow-up, adjusted for clinically relevant covariates (specified above). For the secondary analyses, similar models were used to examine the associations between age of cow milk introduction and volume of cow milk consumed and BMI z score adjusted for the same covariates, except maternal BMI was included instead of maternal height.
Missing data for outcome and all covariate was 1.6% and <10%, respectively. Data were assumed to be missing at random. To reduce bias introduced from missing data, multiple imputation was performed to impute missing data for all covariate and outcome measures [75]. Five data sets were imputed, and the results were combined to obtain pooled estimates and standard errors [76, 77]. All models were assessed for non-linearity using linear splines [78]. A \( p \)-value of less than 0.05 was considered statistically significant, and all covariates remained in the final model regardless of statistical significance [75]. All statistical analyses were carried out using R version 3.5.1 (www.R-project.org)

1.4. Results

A total of 3432 children met the inclusion criteria at baseline. Age of cow milk introduction was missing for 104 children who were excluded, as were 1042 children who had not been introduced to cow milk by the follow-up visit. Some reasons for not consuming cow milk included an intolerance or allergy to cow milk \((n=37)\), the child did not like the taste of cow milk \((n=2)\) and consumption of alternative milk beverage such as almond or soy milk \((n=136)\). Anthropometric data at age 3 to 5 years were available for 1903 \((80\%)\) children who were included in the analysis (Figure 1).

Baseline characteristics of the participants are presented in Table 1. Of the 1903 children \((1022\) boys and 881 girls\) included in the analyses, the mean \((\pm \text{SD})\) age at baseline was 17.2 \((\pm 4.3)\) months. The average age of cow milk introduction was 11.7 \((\pm 2.0)\) (min 5 months; max 30 months). Cow milk was introduced to 71 \((3.7\%)\) children before 9 months, 546 \((28.7\%)\) between 9 and 12 months, 1081 \((56.8\%)\) at 12 months, 160 \((8.4\%)\) between 12 and 18 months and 45 \((2.4\%)\) at 18 months or later. The mean age at follow-up was 3.9 \((\pm 0.6)\) years and the average
length of follow-up was 2.5 years. At follow-up, the mean height-for-age z score was 0.04 (± 0.9), the mean BMI z score was 0.23 (± 0.9) and children consumed on average 1.8 (± 0.9) cups of cow milk per day.

The results of the primary and secondary analyses are presented in Table 2. After adjusting for potential confounders, there was a statistically significant association between a younger age of cow milk introduction and greater height ($p < 0.001$). Each month earlier that cow milk was introduced was associated with a 0.03 higher height-for-age z score (95% CI: 0.05; 0.01) or 0.1 cm per month (95% CI: 0.11; 0.16 cm). At 4 years of age, the difference between a child introduced to cow milk at 9 months relative to 12 months was 0.1 z score units (95% CI: 0.17; 0.05) or 0.4 cm (95 CI: 0.39; 0.51 cm) and relative to 18 months was 0.3 z score units (95% CI: 0.12; 0.46) or 1.2 cm (95% CI: 1.1; 1.4). In the secondary analysis, there was no statistically significant association between age of cow milk introduction and volume of cow milk consumed ($p = 0.90$) or BMI z score ($p = 0.20$) at follow-up.

Exploration for nonlinearity revealed that age of cow milk introduction was associated child height after 9 months of age but not before ($p <0.05$) (Figure 2). Non-linearity was not observed for the relationship between age of cow milk introduction and child adiposity ($p = 0.49$)

1.5. Discussion

In this prospective cohort study of 1903 healthy Canadian children followed for an average of 2.5 years, children who started to consume cow milk at a younger age appeared to be taller by 3-5 years of age. For example, a 4-year-old child introduced to cow milk at 9 months was, on average, 0.4 cm taller compared to a child introduced to cow milk at 12 months, and 1.2 cm taller
compared to a child introduced at 18 months. At 4 years of age, a height difference of 1.2 cm is about one-third of the distance between major percentile lines on the WHO growth charts [30]. This association was found after 9 months of age, but not before, suggesting no additional height benefit for introducing cow milk before 9 months of age. There was no statistically significant association between timing of cow milk introduction and volume of cow milk consumed or adiposity, suggesting that delaying the introduction of cow milk appears unlikely to protect against child obesity.

These results suggest that introducing cow milk as early as 9 months may be appropriate for supporting linear growth without increasing later cow milk consumption or adversely affecting adiposity. Several studies have identified that children who regularly consume cow milk tend to be taller than those who do not [6, 7, 79]. DeBoer et al., using prospectively collected data, observed that 4-year-old children consuming greater amounts of cow milk were taller, and remained taller when measured one year later. At age 4 years, children consuming ≥ 4 versus < 1 milk serving per day were 1 cm taller [79], which is similar to the height difference observed in the current study between children introduced to cow milk at 9 versus 18 months (1.2 cm).

The biological mechanism by which cow milk promotes linear growth is unknown. It has been hypothesized that insulin-like growth factor-1 (IGF-1) naturally present in cow milk may stimulate bone growth. Studies in children have shown that serum IGF-1 levels rise following cow milk consumption, and higher IGF-1 levels during childhood have been proposed to contribute to gains in height [7, 58, 68]. In a cross-sectional study of 90 healthy 2.5-year-old Danish children, higher cow milk intake was positively associated with both height and IGF-1 levels [7]. A longer duration of exposure to higher IGF-1 levels during a period important for
linear growth, as a result of cow milk being introduced at a younger age, may explain the observed association between earlier cow milk intake and greater height in later childhood. The exact age at which IGF-1 exerts an influence on linear growth is not known, but it has been proposed to begin sometime around 9 months of age [80]. This may explain why an association between age of cow milk introduction and height was not observed before 9 months of age. Another explanation might be that there were too few children introduced to cow milk before 9 months of age to detect a relationship. Studies with larger sample sizes would be needed to examine this finding further.

Others have speculated that the relationship between cow milk intake and height may be related to calcium and vitamin D status [46, 61]. Cow milk is a convenient and reliable source of calcium and vitamin D in children’s diet [39, 46]. Ensuring adequate intake of these nutrients in the absence of milk can be challenging and may require careful planning, particularly for young children [5, 81]. Work from our group has found that consumption of milk alternatives was associated with lower vitamin D stores [82]. Providing cow milk at a younger age may increase calcium and vitamin D dietary intake during a time of rapid growth and increased nutritional needs, which may explain the observed association with height.

Finally, it is known that children who do not consume cow milk tend to be shorter [46, 61]. Consumption of non-cow milk beverages (e.g. almond, rice, oat and soy ‘milk’) has been previously associated with lower childhood height [61]. Some have speculated that isoflavones contained in soy milk beverages may limit linear growth [83]. The addition of cow milk into the child’s diet at a younger age may displace consumption of plant-based milk alternatives (e.g. soy, rice or almond ‘milk’) or SSB consumption (e.g. juice, soda), which may positively
influence height. Future research is needed to understand the biological mechanism by which earlier cow milk intake may influence linear growth.

Several observational studies have identified that greater milk intake was associated with higher adiposity in children [6, 10]. In the current study, children who were introduced to cow milk at a younger age consumed similar amounts of cow milk and had similar adiposity at follow-up compared to those introduced to cow milk at an older age. One explanation for these findings may be that introducing cow milk earlier in life but may not promote excess cow milk consumption or increase energy intake. Children may self-regulate their caloric intake following cow milk consumption, which is believed to promote satiety [84]. For example, in a randomized trial of 10-12-year-old children, consumption of cow milk with breakfast, compared to juice, increased satiety and reduced energy intake at the following meal [84].

This study had a number of strengths including the prospective design, with a mean follow-up duration of 2.5 years, which minimized the risk of reverse causality. Other strengths included a relatively large sample of healthy preschool-aged children and detailed questionnaire data which allowed for adjustment of numerous clinically relevant covariates. Although the degree of missing data was low (<10% for all variables) multiple imputation was performed to minimize the risk of bias introduced from missing data.

The study did, however, have several limitations. Although the prospective design took into account the temporal relationship between age of cow milk introduction and child growth, causality cannot be inferred due to the observational nature of the study. Also, the primary exposure measurement relied on parental report of cow milk introduction, which may be subject
to recall bias. However, to minimize the duration of recall, exposure data were collected at the first visit following milk introduction. Confounding by indication is also a possibility whereby parents of smaller children may have delayed or advanced the introduction of cow milk to increase growth. However, children introduced to cow milk earlier seemed similar at baseline to children introduced later. Another limitation was that volume of cow milk consumed at the time of introduction was not measured, which may have been a potential source of bias. Although, children introduced to cow milk at an older age may consume higher volumes of cow milk than children introduced at a younger age, which would have biased our findings in the opposite direction to what was observed. Further, it is possible that ‘bigger’ children were given more milk because of increased hunger or parental perception of the child’s hunger. While the study population was ethnically diverse, it might not be representative of urban children in other settings. Lastly, although adjustment included many potential confounders, residual confounding is a possibility from unmeasured or unknown factors. For example, we were unable to account for dietary factors such as total caloric or protein intake which may have contributed to height differences. Although, previous research found that adjustment for energy and protein intake does not seem to attenuate the association between cow milk intake and height [8]. Lastly, it is unclear whether childhood height is associated with final attained height in adulthood or whether the advantages of being taller outweigh the potential disadvantages including a potential increase in cancer risk later in life [85]. Longitudinal studies that follow children through adulthood are needed to understand whether the association between earlier cow milk intake and childhood height is associated with final attained height in adulthood and the positive and negative long-term impact of the associations observed in this research.
In this cohort of healthy children, a younger age of cow milk introduction was associated with greater height at 3 to 5 years of age, with no apparent benefit of introducing cow milk before 9 months of age. Timing of cow milk introduction did not appear to influence cow milk consumption later in life or adiposity, suggesting the delaying the introduction of cow milk appears unlikely to protect against child obesity. These findings suggest that Canadian recommendations for cow milk introduction as early as 9 months appear appropriate for maximizing child height, without increasing the risk of excess cow milk consumption or adiposity in later childhood. These findings from this study may be important for parents, healthcare professionals and policy makers when considering when to introduce cow milk.
### TABLES AND FIGURES

**Table 4**: Baseline characteristics of participants

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>All participants (n = 1903)</th>
<th>Age of cow milk introduction</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>&lt;12 months (n = 617)</td>
<td>≥ 12 months (n = 1286)</td>
</tr>
<tr>
<td><strong>Characteristics</strong></td>
<td>Mean (± SD)</td>
<td>Mean (± SD)</td>
<td>Mean (± SD)</td>
</tr>
<tr>
<td>Child age (months)</td>
<td>17.2 ± 4.3</td>
<td>14.8 ± 3.8</td>
<td>17.3 ± 4.1</td>
</tr>
<tr>
<td>Male gender, n (%)</td>
<td>1022 (53.6)</td>
<td>330 (53.4)</td>
<td>691 (53.7)</td>
</tr>
<tr>
<td>Age of cow milk introduction (months)</td>
<td>11.7 ± 2.0</td>
<td>9.9 ± 1.4</td>
<td>12.4 ± 1.7</td>
</tr>
<tr>
<td>Birth weight (kg)</td>
<td>3.31 ± 0.6</td>
<td>3.36 ± 0.5</td>
<td>3.28 ± 0.6</td>
</tr>
<tr>
<td>Maternal height (cm)</td>
<td>164.8 ± 6.7</td>
<td>165.2 ± 6.7</td>
<td>164.6 ± 6.6</td>
</tr>
<tr>
<td>Maternal BMI (kg/m²)</td>
<td>24.6 ± 4.6</td>
<td>24.8 ± 4.7</td>
<td>24.5 ± 4.6</td>
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<tr>
<td>Maternal ethnicity, n (%)</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>European</td>
<td>1290 (67.8)</td>
<td>444 (71.9)</td>
<td>846 (65.8)</td>
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<td>Asian</td>
<td>280 (14.7)</td>
<td>76 (12.3)</td>
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<td>African</td>
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<td>Hispanic</td>
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<td>46 (3.6)</td>
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<td>Mixed</td>
<td>89 (4.7)</td>
<td>30 (4.9)</td>
<td>59 (4.6)</td>
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<td>After tax family income, n (%)</td>
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<td>&lt; $30,000</td>
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<td>207 (33.5)</td>
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<td>≥ $150,000</td>
<td>910 (47.8)</td>
<td>301 (48.8)</td>
<td>609 (47.4)</td>
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</table>
Table 5: Association between age of cow milk introduction, height, BMI and volume of milk

<table>
<thead>
<tr>
<th></th>
<th>Unadjusted</th>
<th>Adjusted²</th>
<th></th>
<th>Adjusted³</th>
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<tbody>
<tr>
<td></td>
<td>Effect size (95% CI)</td>
<td>p-value</td>
<td>Effect size (95% CI)</td>
<td>p-value</td>
</tr>
<tr>
<td><strong>Height-for-age z-score</strong></td>
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<tr>
<td></td>
<td>-0.046 (-0.067, -0.025)</td>
<td>1.64 e-05***</td>
<td>-0.034 (-0.055, -0.014)</td>
<td>5.80 e-04***</td>
</tr>
<tr>
<td><strong>Volume of cow milk consumed</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>-0.003 (-0.02, 0.19)</td>
<td>0.76</td>
<td>-0.001 (-0.025, 0.021)</td>
<td>0.90</td>
</tr>
<tr>
<td><strong>BMI z-score</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.006 (-0.014, 0.026)</td>
<td>0.52</td>
<td>0.013 (-0.007, 0.032)</td>
<td>0.20</td>
</tr>
</tbody>
</table>

1 Results from the primary and secondary analysis (n = 1903)

2 Adjusted for age, sex, birth weight, breastfeeding duration, maternal ethnicity, household income, BMI z score, SSB consumption and maternal height

3 Adjusted for age, sex, birth weight, breastfeeding duration, maternal ethnicity, household income, SSB consumption and maternal BMI
Figure 4: Flow chart of participant selection

Eligible children ≤ 2 years of age  
n = 3432

Children who consumed cow milk  
n = 2390

- Reasons for not consuming cow milk:
  - Intolerance or allergy to cow milk (n=37)
  - Consume non-cow milk beverages (n=136)
  - Dislike the taste of cow milk (n=2)

- Missing primary exposure data (n=104)

Children with a follow-up visit at age 3 to 5  
n = 1903

- Follow-up visit at age 3 to 5 not available (n=487)
**Figure 5:** Nonlinear relationship between age of cow milk introduction and childhood height

Age of cow milk introduction and childhood growth

1Nonlinear relationship between age of milk introduction (at baseline) and childhood height (at follow-up); the dashed lines represents 95% CIs
Figure 6: Conceptual model

Conceptual Model

- **Primary exposure:**
  - Age of cow milk introduction

- **Primary outcome:**
  - Height
  - **Secondary outcomes:**
    - (1) Volume of cow milk
    - (2) BMI

- **Confounders:**
  - Child age
  - Household family income
  - Maternal ethnicity
  - Total breastfeeding duration
  - Sugar beverage consumption

- **Predictors of outcomes:**
  - Child gender
  - Birth weight
  - Maternal BMI
  - Maternal height
CHAPTER 4: OVERALL DISCUSSION

The focus of this thesis was to evaluate the relationship between the age of cow milk introduction and childhood growth in a cohort of healthy Canadian children. Considering that the majority of young children in Canada consume cow milk daily [3] understanding factors related to cow milk consumption, such as timing of introduction, has the potential to improve the health and nutrition of Canadian children.

The Nutrition Committee of the Canadian Paediatric Society recommends cow milk as an important source of nutrients for growing children [5]. International guidelines, such as those from the American Academy of Pediatrics, also recommend daily consumption of cow milk for proper growth and development [11, 38]. Previous research suggests that cow milk intake during childhood may promote linear growth [6, 7, 9], but may also accelerate weight gain [10]. Based on these findings, I hypothesized that children who start to consume cow milk at a younger age would be taller but also heavier by 3-5 years of age.

In the present study, the majority of Canadian children were introduced to cow milk between 9 and 12 months of age, in keeping with current Canadian recommendations, while 11% of parents delayed introduction of cow milk beyond age 12 months. Little is known how timing of cow milk introduction might influence growth in later childhood. Through this research, I identified that children who started to consume cow milk earlier in life were taller by age 3 to 5 years. For example, a 4-year-old child introduced to cow milk at 9 months was 1.2 cm taller compared to a child introduced to cow milk at 18 months. At 4 years of age, a height difference of 1.2 cm is about one-third of the distance between major percentiles on the WHO growth
charts [30]. I also identified that the association was non-linear and that there was no additional benefit on height from introducing cow milk before 9 months of age.

In the present study, consumption of cow milk earlier in life contributed to gains in height, a finding supporting earlier investigations. A 2012 meta-analysis of intervention studies from around the world (e.g. Europe, US, China, Vietnam, Kenya, Indonesia and India) observed that children aged 3 to 13 years who consumed an additional 245 ml of cow milk daily grew 0.4 cm taller the following year [9]. Observational studies focusing on generally well-nourished preschool children (<5 years of age) have observed similar findings [6-8]. For example, DeBoer et al. (2015) observed that among children drinking cow milk at 4 years of age, those who consumed ≥ 4 servings of milk daily were 1 cm taller compared to children who consumed less than 1 serving daily [6]. Similarly, Wiley (2009) identified that 2-5 year old children who consumed cow milk daily were 1 cm taller compared to those who did not [8]. Finally, among well-nourished 2.5-year-old Danish children greater milk intake was positively associated with serum IGF-1 levels and with height [7].

Children who do not consume cow milk also tend to be shorter [46, 61]. In a study of 90 children aged 3 to 10 years from New Zealand, cow milk avoidance was associated with shorter stature [46]. Similarly, in a large cross-sectional analysis (n = 5034) from our group of healthy children 2 to 6 years of age living in Toronto, Canada, children who consumed 3 cups of non-cow milk (e.g. almond, oat and soy ‘milk’) were, on average, 1.5 cm shorter compared to children who consumed 3 cups of cow milk [61]. The authors speculated that since milk alternatives tend to be lower in protein, the children may not have received adequate amounts of protein to support optimal growth. Hoppe et al. [7] further suggested that the type of protein may be of importance,
finding that children who consumed plant-based protein (e.g. legumes, nuts) were slightly shorter (0.1 cm) compared to children who consumed animal-based protein (e.g. cow milk).

The component in cow milk that contributes to height is unknown. Most studies from developed countries have focused on dietary calcium and IGF-1 [7, 8, 46, 68]. Since dietary calcium is important for bone growth, adequate calcium intake is considered essential for normal linear growth [60]. In the study by Wiley (2009) adjusting for calcium intake attenuated the magnitude of the association between milk intake and height, suggesting that calcium may play, at least some role, in contributing to growth in height [8]. However, the association between cow milk intake and height remained significant even after controlling for dietary calcium intake, which suggests that there may be a component unique to milk that contributes to height, that is independent of calcium. Researchers have hypothesized that IGF-1 naturally present in cow milk may mediate the relationship between milk intake and height [7, 58]. Studies by Hoppe and colleagues in young children have shown that drinking cow milk increased serum IGF-1 levels and that IGF-1 promotes growth in height [7, 58].

Findings from my thesis are consistent with the current literature which supports cow milk’s role in promoting linear growth in childhood, but extend previous observations, suggesting that the timing of cow milk introduction may be also be critical for maximizing height. Little is known about how timing of cow milk introduction might influence growth in later childhood. In a cross-sectional analysis of NHANES data of American children 2 to 5 years of age, consumption of cow milk before one year of age had no relationship with height [8]. This finding is at odds with my results. One explanation for the discrepancy could be due to differences in study design (i.e. cross-sectional versus prospective). In cross-sectional studies, recall bias can be problematic,
because the exposure of interest occurred long time ago and parental recall of when cow milk was introduced may be inaccurate several years later. In my prospective study, recall bias was minimized by asking parents to report the age the child started drinking cow milk at the first visit following introduction, which was on average 5.3 months later. Further, in the cross-sectional study by Wiley, the child’s age at introduction to cow milk was dichotomized at one year of age; whereas, in my study age of cow milk introduction was measured as a continuous variable. Several problems may arise when continuous variables are dichotomized. One, it may lead to a loss of information, which can reduce the statistical power to detect a true relationship [86]. Second, dichotomizing a variable does not capture the variability within each group. For example, individuals close to, but on the opposite sides of the cut-point, are characterized into different groups, despite being more similar than different [86].

**Biological mechanisms**

One possible explanation for the findings in my thesis is that introducing cow milk earlier in life may be associated with a longer duration of exposure to the growth-promoting properties of cow milk (e.g. calcium, IGF-1), which may positively influence childhood height. It is also possible that starting to consume cow milk at a younger age may displace consumption of plant-based milk alternatives (e.g. almond and rice ‘milk’) during the second year of life. Plant-based beverages (e.g. almond and rice ‘milk’) vary in their nutritional content and therefore are not considered appropriate alternatives to cow milk in children younger than 2 years of age and have previously been associated with lower childhood height. Another explanation for my findings may be reverse causality. Since cow milk is believed to promote growth, reverse causality may occur whereby ‘bigger’ children may be weaner and transitioned to cow milk at a younger age. However, prior to this thesis, a relationship between earlier cow milk introduction and linear
growth had not been described. The opposite may also be possible where parents of ‘smaller’ children may introduce cow milk at a younger age, with the motivation of enhancing growth. However, the prospective design of this study makes reverse causality less likely since measurement of the exposure preceded the outcome.

The finding that the association with height was significant after 9 months of age but not before is consistent with current Canadian guidelines. One explanation for this finding is that there may be periods of growth which are more sensitive to the growth enhancing effects of IGF-1. It has been suggested that growth during the first year of life is less sensitive to IGF-1 than growth in the second year of life [80]. While the exact age when IGF-1 begins to stimulate growth is unknown, it appears to start sometime after 9 months of age [80]. Another explanation might be that there were too few children introduced to cow milk before 9 months of age to detect a relationship with height. In the population which I studied there were 87 (3.7%) children introduced to cow milk before 9 months of age.

The finding that children introduced to cow milk at a younger age seemed to have similar adiposity as children introduced at an older age was surprising. Given that breastfeeding is recommended for obesity prevention [87], I hypothesized that delaying cow milk introduction would be associated with lower adiposity as it may extend the duration of breastfeeding. One possible explanation for this discrepancy may be that the benefits of breastfeeding on obesity plateau after a certain age. A 2005 meta-analysis of 17 published studies from developed countries by Harder and colleagues found that each additional month of breastfeeding was associated with a 4% reduced risk of later obesity; however, this benefit plateaued after 9 months of breastfeeding consistent with findings from my study [87]. The reasons for this plateau are not
known. Another explanation is that the timing of cow milk introduction may not affect the volume of cow milk consumed in later childhood or increase total caloric intake which is in keeping with my findings.

Future research

My research has raised a number of questions. First, the mechanism by which earlier cow milk intake might stimulate linear growth remains unknown. Future observational studies with more detailed dietary information would be helpful in evaluating whether total energy or protein intake is higher in children who start consuming milk at a younger age. Also, measurement of IGF-1 at the time of cow milk introduction may help delineate the role of IGF-1 in these relationships. Understanding the reasons parents introduce cow milk at a younger age may provide insight about reverse causality. To evaluate whether the age of cow milk introduction is causally related to linear growth, a randomized study could be conducted where children would be randomized to start consuming cow milk at 9 months versus 12 months and followed over time to evaluate the effect on growth. Finally, longitudinal studies are needed to understand the long-term effect of earlier milk intake on other health outcomes later in life, as well as the long-term impact of childhood height on final attained height in adulthood.

Strengths and limitations

Strengths of the study include the prospective design, which provided a means of assessing temporal relationships. Because data on age of cow milk introduction was collected before the outcome measurement, child’s growth at follow-up could not have affected parental recall of the exposure, minimizing recall bias and reverse causality. Other strengths included a relatively large multicultural sample of healthy Canadian children seen in routine healthcare settings, which may be representative of other urban children who receive primary healthcare. Detailed questionnaire
data was collected allowing for the adjustment of many potential confounders. Further, I used a sophisticated analytical approach including multiple imputation to address missing data as well as assessment for nonlinearity of the observed relationships. Lastly, all hypothesis tested were determined *a priori*, and the analytic plan was pre-specified, providing a systematic and reproducible approach to conducting this research.

This research does, however, have a number of limitations. First, observational studies cannot determine causality; they can only describe an association. Second, the study relied on parental report of cow milk introduction, which may be subject to social desirability and recall bias. However, in an attempt to minimize error due to poor recall of past exposure I used the first visit following cow milk introduction. Third, I was unable to quantify the amount of cow milk consumed at the time of introduction due to data limitations. This may have influenced findings because volume of milk at the time of introduction may have modified the relationship between the age of cow milk introduction and childhood height. Fourth, this population may not be generalizable to all urban Canadian children as it was primarily a population of children born to highly educated mothers. Although numerous potential confounders were included in the adjusted models, it is possible there may be residual confounding by unmeasured or unknown factors. Lastly, it is unclear whether greater childhood height results in greater adult height or whether the advantages of greater height in adulthood outweigh potential disadvantages including a potential increase in cancer risk [85].

This study suggests earlier cow milk consumption may contribute to gains in height, without adversely affecting child adiposity. These findings support Canadian recommendations for daily cow milk consumption starting around 9-12 months of age. Although the long-term effects of
earlier milk consumption on health outcomes later in life are unclear at this time, cow milk is a convenient source of nutrients which appear to support linear growth in children. Further, cow milk consumption does not appear to influence a child’s risk of later obesity suggesting that the risk of over nutrition from earlier introduction of cow milk is low. My hope is that this research will create dialogue among pediatricians, dietitians and parents about the optimal age of cow milk introduction, stimulate future research and inform nutritional child health policy recommendations.
CHAPTER 5: CONCLUSION

I have identified that children who started consuming cow milk at a younger age appeared to be taller by 3-5 years of age. The association with height was non-linear, suggesting no additional benefit from introducing cow milk before the minimum recommended age of 9 months. I also observed that timing of cow milk introduction was unrelated to volume of cow milk consumed or adiposity at follow-up, suggesting that earlier or later introduction of cow milk appears unlikely to protect against child obesity. Future longitudinal studies which follow children through adulthood are needed to understand the long-term impact of the association observed in this research. Randomized studies which examine height differences following cow milk introduction at 9 versus 12 months of age would be helpful to understand causality in the relationship between earlier cow milk intake and greater childhood height.

Based on the findings in the current study, Canadian recommendations for cow milk introduction as early as 9 months appear to be appropriate for maximizing linear growth in children, without increasing the risk of excess cow milk intake or adiposity in later childhood. These findings will have relevance to a wide audience of parents, healthcare professionals and policy makers who are interested in optimizing children’s growth.
CHAPTER 6: APPENDIX

APPENDIX 1: WHO Child Growth Standards for boys aged 2 to 5 years

![Height-for-age BOYS graph](image-url)
APPENDIX 2: WHO Child Growth Standards for girls aged 2 to 5 year
CHAPTER 7: REFERENCES

20. Rourke Baby Record.
70. Canadian Community Health Survey. 2013, Statistics Canada: Ottawa, ON.