PREDICTORS OF 25-HYDROXYVITAMIN D SERUM CONCENTRATIONS AMONG NON-WESTERN IMMIGRANT PRESCHOOL CHILDREN

by

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A thesis submitted in conformity with the requirements for the degree of Master of Science

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Predictors of 25-hydroxyvitamin D serum concentrations among non-western immigrant preschool children

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ABSTRACT

We determined whether children older than 1 year from non-western immigrant families had lower serum 25-hydroxyvitamin D levels than children from western born families. Children ages 1-6 years were recruited through the TARGet Kids! practice based research network. Univariable analysis revealed that non-western immigrant children had 4 nmol/L lower 25-hydroxyvitamin D (p=0.006; 95% CI: 1.4-8.0) and increased odds of 25-hydroxyvitamin D <50 nmol/L (OR 1.9, 95% CI:1.3–2.9). After adjustment for known vitamin D determinants, cow’s milk intake, vitamin D supplements, season and age were significant covariates and current vitamin D supplementation had the strongest confounding effect. In order to use the ethnicity variable, we developed a new standardized geographically based closed-ended ethnicity question, which was a practical alternative to the widely used open-ended ethnicity questions. There was an association between non-western immigration and lower 25-hydroxyvitamin D in early childhood and this appears primarily related to known vitamin D determinants.
ACKNOWLEDGEMENTS

Completing my master’s has been a wonderful experience. I feel extremely lucky to have worked with and will continue to work with the TARGet Kids! research team, as they are an encouraging and supportive group. I would first like to thank my supervisors: Dr. Jonathon Maguire for his optimism and inspiring me to believe that anything is possible. For motivating me to continue down the path of discovery and opening a door for me into an exciting future. Dr. Pauline Darling for her amazing positive feedback and frequently encouraging my dreams while grounding me to what is feasible.

Thank you to the entire TARGet Kids! team for creating an environment that encouraged learning beyond my individual project. I thoroughly enjoy our regular scientific meetings as they helped me gain confidence as a dietitian researcher and a valued member of the team, while stimulating ideas for future projects.

To all those who helped facilitate this study, including all the children and families who have enrolled in TARGet Kids! and spent their time completing the many questionnaires as well as the practitioners at the paediatric and family medicine practices. To the research manager (Marina), coordinators (Sarah and Julie) and assistants (Tonya, Juela, Kanthi, Laurie, Subitha and Tarandeep) as members of the extensive TARGet Kids! family, my project would not have been possible without your hard work and dedication to improving the health of children. Thanks to the ongoing support of my committee members Dr. Patricia Parkin, Dr. Catherine Birken, Dr. Deborah O’Connor and Dr. Valerie Tarasuk.

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LIST OF ABBREVIATIONS

AAP  American Academy of Paediatrics
AHRC  Applied Health Research Centre
BMI  Body Mass Index
CCHS  Canadian Community Health Survey
CHMS  Canadian Health Measures Survey
CPS  Canadian Paediatric Society
DRI  Dietary Reference Intakes
EAR  Estimate Average Requirement
FDR  Food and Drug Regulation
FNB  Food and Nutrition Board
IOM  Institute of Medicine
IU  International Units
NHANES  National Health and Nutrition Examination Survey
OR  Odds ratio
PORT  Paediatric Outcomes Research Team
PTH  Parathyroid Hormone
RDA  Recommended Dietary Allowance
SD  Standard deviation
UL  Tolerable upper intake level
VIF  Variance inflation factor
WHO  World Health Organization
LIST OF DEFINITIONS

**Non-western**: Individual not born in Europe, North America, Australia or New Zealand.\textsuperscript{123,124}

**Dietary Reference Intakes**: is a set of nutrient reference values for healthy populations (including different age and sex groups) that can be used for assessing and planning diets.\textsuperscript{6}

**Serum 25-hydroxyvitamin D**: is thought to reflect total body vitamin D stores from all sources (cutaneous synthesis and dietary intake).\textsuperscript{6}
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STUDENT CONTRIBUTIONS

• Conceptualized and designed the research studies

• Categorized ethnicity for the entire TARGet Kids! database. Converted the open-ended variable from Canadian census into a new geographically based closed ended ethnicity question, for maternal, paternal and child’s self identified ethnicity.

• Met with ethnicity experts (Marcel Urquia through the Li KaShing Knowledge Institute and Toronto Public Health) to develop the most appropriate categorization of geographical ethnicity for ancestral origin

• Evaluated the reclassification of ethnicity

• Recruited study participants into TARGet Kids! at three St. Michael’s Hospital sites (Pediatric Ambulatory clinic, 61 Queen St. East; Family Health Team, 410 Sherbourne St.; and Family practice, 80 Bond St.)

• Performed statistical analysis using SAS 9.0

• Presented research findings at two National Research conferences: Canadian Nutrition Society (Vancouver BC) and Canadian Pediatrics Society (London ON)

• Wrote thesis

• Submitted research study for publication at Public Health Nutrition and International Journal of Epidemiology
CHAPTER 1 INTRODUCTION

1.0: Introduction

Micronutrient and macronutrient sufficiency plays a fundamental role in achieving optimal growth and development of children.\textsuperscript{1,2} Dietary problems that occur in childhood are believed to impact on children’s growth and health status later in life.\textsuperscript{3} As the health care system evolves towards prevention of disease rather than treatment, understanding predictors of children’s nutritional status and identifying high-risk populations is important.\textsuperscript{4,5}

Vitamin D may play an important role for optimizing child health.\textsuperscript{6} The American Academy of Pediatrics (AAP) and the Institute of Medicine (IOM) recommend that 25-hydroxyvitamin D concentrations in children should be above 50 nmol/L in order to avoid rickets.\textsuperscript{6,7} The Canadian Paediatric Society (CPS) recommends that 25-hydroxyvitamin D levels should be above 75 nmol/L for optimal health.\textsuperscript{8} Observational epidemiological studies have suggested that low levels of vitamin D may play a role in fractures\textsuperscript{9,10}, asthma\textsuperscript{11,12}, respiratory infections\textsuperscript{13} and obesity in children.\textsuperscript{14} These are some of the most common health issues in childhood and have a significant economic impact on the health care system.\textsuperscript{15,16}

It is known that children obtain vitamin D from two sources, endogenous cutaneous synthesis through exposure to ultraviolet B (UVB) rays and exogenous dietary intake. However, according to data from the United States National Health and Nutrition Examination Survey (NHANES) 2001-2004, many children have 25-hydroxyvitmain D levels below predefined cut points: 14\% and 48\% of children ages 1-5 years have circulating 25-hydroxyvitamin D below 50 nmol/L and 75 nmol/L respectively, making this a concerning issue.\textsuperscript{17} A number of predictors of low 25-hydroxyvitamin D have been identified including skin pigmentation, breastfeeding...
without vitamin D supplementation, lower cow’s milk intake, higher latitude, winter season, and higher Body Mass Index (BMI).

Toronto is the most ethnically diverse city in Canada with immigrants accounting for 45.7% of the population according to the 2006 census. Epidemiological data from the Canadian Paediatric Surveillance Program has suggested that children under 1 year of age from immigrant non-western families (i.e. immigrating from a country other than Europe, North America, Australia or New Zealand) are at risk of vitamin D deficiency rickets. Understanding the impact of immigration on 25-hydroxyvitamin D may help to identify children at risk of low 25-hydroxyvitamin D and therefore provide an opportunity for early intervention.

Self-reporting ethnicity in an open-ended format is commonly used in national censuses including Statistics Canada Census and NHANES. However open-ended questions are subject to an individual’s understanding of the question and introduce considerable analytic challenges. The open-ended ethnicity variable was reclassified into a geographically based closed ended ethnicity question appropriate for analytic use. In order to understand the impact of immigration from ethnicity we needed to measure these two variables separately.

The purpose of this thesis was to answer the following research questions: 1) to determine whether children older than 1 year from non-western immigrant families have lower serum 25-hydroxyvitamin D levels than children from western born families, 2) to determine which factors influence this relationship, and 3) to evaluate the degree of agreement between the new geographically based closed-ended ethnicity question and the geographically reclassified open-ended variable from Canadian census.

The literature review (Chapter 2) is divided into 4 sections: 1) vitamin D 2) ethnicity and immigration 3) vitamin D deficiency in immigrant populations and 4) summary of literature
review. Chapters 3 and 4 of this thesis describe the studies: *Non-western immigrant children have lower 25-hydroxyvitamin D than children from western born families* and *Measuring Ethnicity in children: a geographic approach*. Chapter 5 is an overall discussion; Chapter 6 describes the conclusions and future directions; Chapter 7 contains the references and Chapter 8 the appendices.
CHAPTER 2 LITERATURE REVIEW

2.1 Vitamin D

2.1.1 Structure and function

Vitamin D is a fat-soluble vitamin comprised of seco-sterols and is stored in the liver and fat tissue of humans.\(^6\) Vitamin D has two physiological forms: ergocalciferol (vitamin D\(_2\)) and cholecalciferol (vitamin D\(_3\)),\(^6,28\) which differ in their side chain structure but have equal biological activity.\(^6\) Vitamin D\(_2\) is made from the ultraviolet irradiation of ergosterol and is found in plants, yeast and fungi.\(^28,29\) Vitamin D\(_3\) occurs naturally and is produced through ultraviolet light exposure of 7-dehydrocholesterol, which is found naturally in the skin of many animals including humans.\(^20,30\) Vitamin D\(_2\) and D\(_3\) are precursor molecules to the active form of vitamin D called calcitriol and are biologically inactive until they experience two hydroxylation reactions.\(^6\) The first step of activation occurs in the liver by adding a hydroxyl group to form 25-dihydroxyvitamin D (25(OH)D); the second step occurs in the kidney where another hydroxyl group is added to form 1,25-dihydroxyvitamin D or calcitriol (1,25(OH)\(_2\)D).\(^28\)

![Chemical structure of calcitriol](image)

**Figure 1:** Chemical structure of calcitriol (1,25-dihydroxyvitamin D)\(^31\)
Calcitriol is essential for all humans in order to attain optimal health. The main physiologic function of vitamin D is to maintain the homeostasis of serum calcium and phosphorus concentrations within a range that supports cellular processes, neuromuscular function, and bone ossification. Vitamin D promotes the absorption of dietary calcium and phosphorus in the small intestine and mobilizes these mineral stores from the bone, playing a critical role in skeletal development and cellular functions. Observational epidemiological data has suggested an association between vitamin D in the body and the risk of health problems including cancer, cardiovascular disease, diabetes and metabolic syndrome, falls and physical performance, immune functioning and autoimmune disorders, infections, neuropsychological functioning, and preeclampsia in adults. According to the IOM vitamin D dietary reference intake (DRI) committee “these potential roles of vitamin D are currently best described as hypotheses of emerging interest, and the conflicting nature of available evidence cannot be used to establish health benefits with any level of confidence”, highlighting these important areas of research.

2.1.2 Sources of Vitamin D

Humans obtain vitamin D through endogenous synthesis in the skin and exogenous dietary sources.

2.1.2.1 Endogenous synthesis

Naturally found in the skin is the precursor molecule 7-Dehydrocholesterol (pre-vitamin D$_3$). Photolysis of 7-Dehydrocholesterol occurs in the epidermis and dermis layers of the skin through ultraviolet B (UVB) radiation between 290 and 315nm. Once in the skin, pre-
vitamin D₃ equilibrates thermally to vitamin D₃, moving from the plasma membrane to the extracellular space and is then attracted to vitamin D binding protein in the circulation and moves into the dermal capillary bed.³⁰ The thermal activation of pre-vitamin D₃ can also lead to other non active vitamin D forms including lumisterol and tachysterol.³³,³⁵,³⁶ This limits the endogenous synthesis of vitamin D₃ through photo-degradation, which is a regulatory mechanism to prevent toxicity with prolonged sun exposure.³³

Sun exposure is a significant source of serum 25-hydroxyvitamin D for many adults living in North America in the summer but this is less of a contributor during the winter months.³³ It has been estimated that adults can synthesize adequate vitamin D from exposure of arms and legs to the sun for 5-30 minutes between the hours of 10 am and 3 pm two times per week (depending season, latitude, and skin pigmentation).²⁹ Adequate sun exposure is not well documented in children, however the CPS recommends that infants and children should be exposed to short periods (less than 15 minutes/day) of sunlight in order allow for cutaneous production of vitamin D while minimizing the possibility of skin damage.⁸ As stated, the body can naturally synthesize vitamin D, but there are many factors which decrease this ability in children including darker skin pigmentation, higher latitude, winter season, higher adiposity; therefore endogenous synthesis is not necessarily a sufficient source of vitamin D (each of these factors will be discussed below, ‘Determinants of 25-hydroxyvitamin D in children’).³⁰,³⁴

2.1.2.2 Exogenous sources

2.1.2.2.1 Natural Sources

Vitamin D is naturally present in fatty fish and small amounts in mushrooms and egg yolk (see appendix B for food sources); however the amount received in humans from naturally
occurring in foods is dependent on factors including the time of year that the food was harvested and the quantity ingested.\textsuperscript{34}

\textbf{2.1.2.2 Fortification}

Due to limited capacity for endogenous synthesis of vitamin D and the scarcity of naturally occurring vitamin D from dietary sources the Canadian government has implemented fortification of food products, cow’s milk and margarine, in order to prevent vitamin D deficiency rickets.\textsuperscript{37} The Food and Drug Regulation (FDR) states that cow’s milk must contain 35–45 international units (IU) of vitamin D per 100 mL and 530 IU per 100 g of margarine (approximately 75 IU/tablespoon [15 mL]).\textsuperscript{37} The FDR in Canada states that infant formula must contain between 40 and 80 IU of vitamin D per 100 kcal.\textsuperscript{37} There is high variability between the levels fortified and the actual amounts present in food products, despite the government’s mandates.\textsuperscript{38–41}

\textbf{2.1.2.3 Supplementation}

If an adequate amount of vitamin D, through dermal synthesis and dietary sources is not attained, supplementation is necessary in order to avoid deficiency.\textsuperscript{2} Supplement products in Canada contain D\textsubscript{2} or D\textsubscript{3} in levels ranging between 400 IU to 1000 IU per daily dose.\textsuperscript{6} Single dose supplements above 1000 IU must be obtained with a prescription.\textsuperscript{6,42} The American Academy of Pediatrics (AAP) Committee on Nutrition recommends that children who are consuming less than 1000 mL/day of vitamin D fortified formula or milk should receive a vitamin D supplement of 400 IU/day.\textsuperscript{7} The Canadian Paediatric Society recommends that children who are breastfed under 1 year of age should be supplemented with 400 IU of vitamin
D daily and infants under six months should not exceed 1000 IU/day.\textsuperscript{8} An updated report by Health Canada (a joint statement of Health Canada, Canadian Paediatric Society, Dietitians of Canada and Breastfeeding Committee for Canada) on Nutrition for Healthy Term Infants states, “Infants who are not exclusively formula-fed should receive a vitamin D supplement of 10\textmu g (400 IU). They should get this amount regardless of their average formula intake. Their total intake from supplement and formula is not likely to exceed the upper level of 25 \textmu g (1000 IU) per day”.\textsuperscript{43} There are no current Canadian recommendations for vitamin D supplementation in children older than 1 year of age.\textsuperscript{8}

There is interest in potentially supplementing lactating women with high dose (2000 IU) vitamin D supplements, in order to increase the vitamin D concentration of breast milk to meet the needs of the infant; however, more research is needed to validate the efficacy and safety of this approach.\textsuperscript{43,44}

2.1.3 Clinical implications and child health outcomes

2.1.3.1 25-hydroxyvitamin D in children

Serum 25-hydroxyvitamin D is thought to reflect total body vitamin D stores from all sources (cutaneous synthesis and dietary intake).\textsuperscript{45}

2.1.3.2 Recommended serum concentrations of 25-hydroxyvitamin D

The American Academy of Pediatrics (AAP) and Institute of Medicine (IOM) recommend that 25-hydroxyvitamin D levels in children should be greater than 50 nmol/L in order to avoid rickets.\textsuperscript{7,45,46} The Canadian Paediatric Society (CPS) has classified 25-hydroxyvitamin D below 50 nmol/L as deficient, between 50 nmol/L and 75 nmol/L as insufficient and above 75 nmol/L
as optimal. The CPS parameters are based on adult data suggesting that parathyroid hormone (PTH), which is a hormone that increases calcium reabsorption from bone, is minimized at 25-hydroxyvitamin D levels greater than 75 nmol/L.

The IOM vitamin D committee used serum 25-hydroxyvitamin D levels from published studies relating to bone health in order to establish 25-hydroxyvitamin D reference ranges, <30 nmol/L and <50 nmol/L as deficient and insufficient respectively. The IOM vitamin D committee concluded that there is need for consensus over the reference ranges for serum 25-hydroxyvitamin D in order to appropriately supplement a population.

### 2.1.3.3 Levels of 25-hydroxyvitamin D in children

The National Health and Nutrition Examination Survey (NHANES) is a national survey in the United States designed to assess the health and nutritional status of a representative sample of adults and children. In 2001-2004, NHANES found that children ages 1-5 years had a mean 25-hydroxyvitamin D concentration of 70 nmol/L (95% CI: 68-73), based on serum collections from 1799 subjects. Furthermore, <1%, 14% and 48% of children ages 1-5 years had serum 25-hydroxyvitamin D concentrations <25 nmol/L, 25-49.9 nmol/L and 50-74.9 nmol/L respectively.

The Canadian Health Measures Survey (CHMS) is a comprehensive national survey, which directly measures the health of Canadians. The 2007-2009 CHMS collected serum 25-hydroxyvitamin D data on individuals age 6 to 79 years. There is no national Canadian data on 25-hydroxyvitamin D concentrations of children under the age of 6 years. The age group closest to our target population, is children age 6-11 years, who had a mean serum 25-hydroxyvitmain D concentration of 75 nmol/L (95% CI: 70.3-79.7), based on serum samples
from approximately 930 subjects.\textsuperscript{52} Fourteen percent of children age 6-11 years had serum 25-hydroxyvitamin D concentrations \(<50\ \text{nmol/L}\).\textsuperscript{52} According to the IOM guidelines approximately 14% of children ages 1-5 years (NHANES) and 6-11 years (CHMS) have insufficient (<50 nmol/L) serum concentrations of 25-hydroxyvitamin D.

\textbf{2.1.3.4 Health problems associated with vitamin D deficiency (<25 nmol/L)}

Severe vitamin D deficiency can lead to impaired mineralization of bone tissue, causing osteomalacia and damage of growth plates, which is evident in children with rickets.\textsuperscript{32} Symptoms of rickets include skeletal deformities, hypocalcemic seizures, delayed developmental milestones and fractures.\textsuperscript{53} A recent study from the Canadian Paediatric Surveillance Program found that over 100 children were diagnosed as having vitamin D deficiency rickets between July 2002 and June 2004.\textsuperscript{32} The majority of these children had one or more of the following risk factors: immigrant to Canada, higher levels of melanin skin pigment, and exclusive breast feeding without vitamin D supplementation.\textsuperscript{32}

\textbf{2.1.3.5 Health problems associated with low 25-hydroxyvitamin D (<50 or <75 nmol/L)}

There is increasing concern regarding the effects of low levels of 25-hydroxyvitamin D and its influence on overall health. \textit{In vitro} research has revealed that vitamin D receptors are located on many tissues throughout the body and are not limited to skeletal and endocrine systems.\textsuperscript{29} This suggests that vitamin D could be acting in other ways within the body.\textsuperscript{29,54} Observational epidemiological studies have suggested that low levels of vitamin D may play a role in fractures\textsuperscript{9,10}, asthma\textsuperscript{11,12}, respiratory infections\textsuperscript{13} and obesity in children.\textsuperscript{14} These are some of the most common health issues in childhood and have a significant economic impact on
the health care system. Further studies are needed to determine whether nutrition interventions aimed at increasing 25-hydroxyvitamin D status impact child health outcomes.

### 2.1.4 Nutritional Recommendations

Recommended intakes of vitamins and minerals are based on the Food and Nutrition Board (FNB) of Health Canada and the United States Institute of Medicine (IOM) guidelines. The Dietary Reference Intakes (DRIs) is a collaborative resource identifying nutrient needs for different sex and age groups. New DRI reports were released by the IOM November 2010, establishing an Estimated Average Requirement (EAR), Recommended Dietary Allowance (RDA) and a new Tolerable Upper Intake Level (UL) for vitamin D and calcium. When creating the DRIs the IOM vitamin D committee assumed a healthy population, a BMI within a normal range and minimal sun exposure. The committee did not include the endogenous source of vitamin D (sun exposure) as a factor in developing the DRI levels due to the risks associated with UVB exposure and skin cancer. The CPS recommends that infants and children should be exposed to short periods (less than 15 minutes/day) of sunlight in order allow for cutaneous production while minimizing the possible skin damage.

#### 2.1.4.1 Dietary reference values and cutoffs

The “Committee to Review Dietary Reference Intakes for Vitamin D and Calcium, Food and Nutrition Board” used available data to link serum 25-hydroxyvitamin D concentrations with total dietary intakes (food and supplements) in order to estimate DRI values.

The IOM vitamin D committee established the vitamin D EAR by using a serum 25-hydroxyvitamin D level of 40 nmol/L, which represents the average requirement of a population.
or one that meets the needs of approximately half the population (50% of the population). The committee used a serum 25-hydroxyvitamin D level of 50 nmol/L in developing the RDA, as the requirement for nearly all of the population (97.5% of the population). For infants (less than 1 year), observational data was used to establish the Adequate Intake (AI) a suggested dose of 400 IU per day was adequate to maintain serum levels between 40-50 nmol/L.

The IOM vitamin D committee found Upper Levels (ULs) difficult to establish due to the lack of data on chronic excess versus single high doses causing intoxication. The committee reviewed available data and ULs were created to maximize public health protection through reducing the risk of toxicity. The vitamin D committee used a starting point of 10,000 IU as it had not been associated with toxicity, and corrected this value for uncertainty and ethnic and racial differences. This adjustment was based on the goal of public health protection by avoiding hypervitaminosis D and other emerging data relating to adverse effects of intakes above the UL. This was then decreased for children ages 0-8 years for precautionary measures.

### 2.1.4.2 Recommended dietary intake levels for children

The EAR and RDA for children ages 1-8 years is 400 IU and 600 IU respectively. The UL is 2500 IU for children 1-3 and 3000 IU for children 4-8 years old. The AI for children under 1 year of age is 400 IU. The UL for children ages 0-6 months and 6-12 months is 1000 IU and 1500 IU respectively (see Appendix C).

Vatanparast et al. in 2010, using data from the Canadian Community Health Survey (CCHS), found that children ages 1-8 years (N=5655) consumed on average 248 IU/day of vitamin D from food. According to a study by Shakur et al. in 2012, using data from CCHS 2.2 (2004), children ages 1-8 years have a high prevalence of vitamin D inadequacy ranging
from 85-94% based on diet alone; however when accounting for supplement use the prevalence of inadequacy reduced to 10%.56

Table 1: Summary of vitamin D recommended dietary intake guidelines

<table>
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<tr>
<th>Source</th>
<th>Target 25-hydroxyvitamin D</th>
<th>Recommended dietary intake</th>
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<tr>
<td>Institute of Medicine (IOM)6</td>
<td>40 nmol/L for EAR</td>
<td>- EAR= 400 IU/day</td>
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<tr>
<td></td>
<td>50 nmol/L for RDA</td>
<td>- RDA= 600 IU/day</td>
</tr>
<tr>
<td>Canadian Pediatric Society (CPS)8</td>
<td>75-225 nmol/L</td>
<td>- Vitamin D supplement containing 400 IU/day for breastfed infants</td>
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<tr>
<td></td>
<td></td>
<td>- If infants are consuming less than 1000 mL of commercial infant formula or fortified milk, they should be taking a vitamin D supplement of 400 IU</td>
</tr>
<tr>
<td>American Academy of Pediatrics (AAP)7</td>
<td>&gt;50 nmol/L</td>
<td>- Breastfed and partially breastfed infants should be supplemented with 400 IU/day</td>
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<td></td>
<td></td>
<td>- Supplementation should be continued unless the infant is weaned to at least 1 L/day of vitamin D fortified formula or whole milk</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- All non breastfed infants, as well as older children who are ingesting &lt;1 L/day of vitamin D fortified formula or milk, should receive a vitamin D supplement of 400 IU/day</td>
</tr>
<tr>
<td>Health Canada (Nutrition for Healthy Term Infants: Recommendations from Birth to Six Months)33</td>
<td>&gt; 50 nmol/L</td>
<td>- Vitamin D supplement containing 400 IU/day for breastfed infants</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Infants who are not exclusively formula-fed should receive a vitamin D supplement of 400 IU. They should get this amount regardless of their average formula intake. Their total intake from supplement and formula is not likely to exceed the upper level of 25 µg (1000 IU) per day</td>
</tr>
</tbody>
</table>

2.1.5 Laboratory measurement of vitamin D status

Calcitriol formation is not directly regulated by synthesis of vitamin D in the skin or dietary intake, as other factors including parathyroid hormone (PTH) help to control serum concentrations.6 Calcitriol has a short half-life (hours) and levels can be normal even when an individual is severely vitamin D deficient.6 Therefore, although calcitriol is the active form of
vitamin D, it is not a good indicator of vitamin D deficiency and thus 25-hydroxyvitamin D is often used to assess vitamin D status.\textsuperscript{6}

2.1.5.1 Measuring levels of 25-hydroxyvitamin D in children

The best method of assessing vitamin D status of children is through measuring serum 25-hydroxyvitamin D, as it has the longest half-life of all the vitamin D derivatives and accumulates in the liver.\textsuperscript{57} Serum 25-hydroxyvitamin D concentrations reflect a combination of the total vitamin D synthesized via UVB exposure and dietary intake of vitamin D\textsubscript{2} and D\textsubscript{3}, representing a biomarker of exposure.\textsuperscript{58} Serum 25-hydroxyvitamin D levels increase in adults in response to increasing vitamin D intake but the relationship is non-linear and depends on participants’ baseline 25-hydroxyvitamin D level (\textless{}40 vs. \textgreater{}40 nmol/L) and the duration of supplementation (\textless{}3 months versus \textgreater{}3 months).\textsuperscript{6}

2.1.6: Determinants of 25-hydroxyvitamin D in children

2.1.6.1 Skin pigmentation

Darker skin pigmentation is associated with a higher level of melanin pigment in the epidermal layer of the skin, which decreases the body’s ability to synthesize vitamin D.\textsuperscript{6,59} Observational epidemiological data suggests that individuals with higher levels of melanin pigment tend to have lower circulating 25-hydroxyvitamin D concentrations compared to those with less melanin pigment.\textsuperscript{29,32,60} A study in 2007 by Armas et al., found that adults with light skin pigmentation (ie. northern Europeans) had a two fold higher serum 25-hydroxyvitamin D concentration compared with adults with dark skin pigmentation (ie. Sub-Saharan African) when exposed to equal levels of UVB doses.\textsuperscript{61}
Ward et al. found that Canadian children with darker skin pigmentation had a higher risk of developing vitamin D deficiency rickets. An American study found that African American women are more likely to enter pregnancy with low levels of 25-hydroxyvitamin D (<37.5 nmol/L), and their children are at a higher risk of vitamin D deficiency rickets.

2.1.6.2 Breast-feeding without vitamin D supplementation

Breast milk contains very little vitamin D making it difficult for an infant who is solely breastfed to acquire adequate levels from their mother; furthermore, women who are vitamin D deficient prior to lactation provide even less vitamin D in breast milk. A Canadian study by Ward et al. in 2007 and an American study by DeLucia et al in 2003, found that 94% and 93% of children with nutritional rickets had been previously or were currently breastfed. A study by Gordon et al. in 2008 in Boston Massachusetts, found a 10-fold increased risk of developing vitamin D deficiency (defined as < 50 nmol/L) between breastfed infants without supplementation and those who were exclusively bottle-fed. There is interest in potentially supplementing lactating women with high dose (2000 IU) vitamin D supplements, in order to increase the vitamin D concentration of breast milk to meet the needs of the infant; however, more research is needed to validate the efficacy and safety of this approach.

An updated 2012 statement released by Health Canada recommends “a daily vitamin D supplement of 10µg (400 IU) for breastfed infants.” and that “Infants who are partially breastfed should receive a vitamin D supplement of 10µg (400 IU). They should get this amount regardless of their average formula intake. Their total intake from supplement and formula is not likely to exceed the upper level of 25 µg (1000 IU) per day.”
2.1.6.3 Low cow’s milk intake

Data from CCHS 2.2 identified that milk products were the source of 75% of the dietary vitamin D intake of children age 1-8 years.\textsuperscript{55} A number of studies have suggested that a low consumption of cow’s milk in infants, children and adolescents, has been associated with lower serum levels of 25-hydroxyvitamin D.\textsuperscript{48,60,65,66}

Kumar et al. in 2009, using NHANES 2001-2004 data, suggested that children consuming milk servings ‘less than daily’ and/or ‘less than weekly’ had an increased likelihood of having vitamin D deficiency, with an odds ratio for low vitamin D concentration (defined as 25-hydroxyvitamin D lower than 37.5 nmol/L) of 2.9 (95% CI: 2.10 to 3.90).\textsuperscript{48}

Gordon et al. in 2004, found that adolescents age 11-18 years who had a higher consumption of cow’s milk were at lower risk of having vitamin D deficiency (< 37.5 nmol/L), with an odds ratio of 0.75 (95% CI: 0.61-0.93).\textsuperscript{60} They also found that serum 25-hydroxyvitamin D concentrations were higher with increased milk consumption.\textsuperscript{60} Another study by Gordon et al. in 2008, found that milk consumption in toddlers age 12 to 24 months significantly decreased the odds of deficiency, with an odds ratio of 0.51 (95% CI: 0.34-0.76) or a 7.75 nmol/L increase in 25-hydroxyvitamin D concentration per cup of cow’s milk.\textsuperscript{65} This is a similar finding to that of Maguire et al. in 2009, suggesting an odds ratio of 0.44 (95% CI: 0.2–0.96) or a 6.9 nmol/L increase in 25-hydroxyvitamin D per 1 cup/day increase in cow’s milk in children age 24-30 months.\textsuperscript{66}

2.1.6.4 Higher latitude and winter months

The number of UVB photons that reach the earth depends on the zenith angle of the sun “the more oblique the angle, the fewer UVB photons reach the earth”\textsuperscript{29,30}; therefore, vitamin D
synthesis through UVB rays decreases as latitude increases. According to the DRIs, during the winter months, above 40 degrees north and below 40 degrees south, synthesis is absent.\textsuperscript{33,67-69} Toronto is located at 43 degrees north and studies have shown that low 25-hydroxyvitamin D is common in children at this latitude.\textsuperscript{60,65}

Sunlight exposure is limited during much of the year in Toronto, due to the city’s temperature and subsequent clothing coverage.\textsuperscript{65} According to a study in Boston (latitude 42 degrees North) there is no dermal production of vitamin D, synthesis from the skin, during the months of November through to April.\textsuperscript{70}

\textbf{2.1.6.5 Higher BMI}

Obesity is a factor that might be related to decreased serum 25-hydroxyvitamin D levels. Studies suggest that vitamin D from both cutaneous (endogenous production) and dietary sources (exogenous) is deposited or sequestered in adipose tissues due to it’s fat soluble structure and is therefore not as bioavailable.\textsuperscript{33,71} Maguire et al. in 2009, suggested an inverse association between BMI and vitamin D in children age 24 to 30 months.\textsuperscript{66} Children with a body mass index (BMI) of 14–15 kg/m\textsuperscript{2} had a 2.6 increased odds (95% CI: 0.8–8.3) and a BMI of 17–18 kg/m\textsuperscript{2} had 1.2 increased odds (95% CI: 0.6–2.6) of having a low (lower than 50 nmol/L) vitamin D concentrations.\textsuperscript{66}

NHANES data indicated that young obese women of European ancestry had lower circulating serum 25-hydroxyvitamin D levels when compared to their leaner counterparts; however they also reported lower use of dietary supplement.\textsuperscript{33} Studies have found that serum 25-hydroxyvitamin D levels increase in individuals experiencing modest weight loss, without a change to vitamin D dietary intake or sun exposure.\textsuperscript{72-75}
2.1.6.6 Other Factors

Lifestyle choices that influence exposure to the sun including clothing coverage and sunscreen use can also be predictors of vitamin D deficiency.\textsuperscript{8,33} Clothing coverage decreases the amount of vitamin D synthesis but the amount of UVB protection depends on the thickness or weave of the fabric.\textsuperscript{69,76} A study in 2008 by Misra et al., found that sunscreen use decreases cutaneous vitamin D synthesis in adults due to the role of protecting the skin from UVA and UVB wavebands which is associated with DNA damage.\textsuperscript{33,77}

Age can have an effect on serum 25-hydroxyvitamin D levels as studies suggest that levels decline in children with increasing age.\textsuperscript{78} Gender differences have been proposed in studies, in which serum 25-hydroxyvitamin D levels are lower in females than in males; however reasons for these differences and whether these differences are observed in children are unclear.\textsuperscript{78-81} Education and food security factors may be related to vitamin D levels, however their impact on children’s 25-hydroxyvitamin D is unknown.\textsuperscript{82}

A review by Renzaho et al. of studies conducted between 1980 through 2010, suggested that ethnic minority children living in United States or New Zealand, are at higher risk of low 25-hydroxyvitamin D (25-hydroxyvitmain <50 nmol/L) versus their white peers, 45% versus 10% respectively.\textsuperscript{83} According to NHANES, non-Hispanic black and Hispanic children ages 1-11 years have lower 25-hydroxyvitamin D than non-Hispanic white children, implying that ethnicity may be a predictor of vitamin D status.\textsuperscript{17} Gozdik et al. found that young adults with East and South Asian backgrounds living in Toronto in the winter had significantly lower 25-hydroxyvitamin D than individuals with European ancestry.\textsuperscript{84}
2.2 Ethnicity and immigration

2.2.1 Classification of Ethnicity: defining Race, Ethnicity and Nationality

Race, ethnicity and nationality are often collected in research studies and used as descriptors in social analysis. Most researchers agree that collecting these data is important for identifying potential variations in disease risk and predictors of health status.

The term race often defines a group based on physical attributes or by biological commonality, for example skin color and other facial features that impact an individual's perceived racial identity. Ethnicity is an alternative to race with less biological associations and incorporates both phenotypical and cultural dimensions. Ethnicity is considered the social group to which an individual belongs and identifies with or is perceived to belong to as a result of shared characteristics including geographic, ancestral origins and cultural commonality (shared beliefs, values and practices). Nationality is viewed as the nation to which an individual currently belongs and is often based on geographic location. All of these constructs aim to describe an individual or group’s origins or ancestry. Many researchers collapse these constructs into a single dimension “race/ethnicity” because the distinction between them is often indistinct and overlapping. However, it has been argued that if data is needed on ethnicity it should be measured directly and not mixed with nationality or race.

2.2.2 Measuring ethnicity

2.2.2.1 National census ethnicity measurement

There is no internationally recognized method of accurately classifying ethnicity. Census and national surveys often collect data on ethnicity, language, religion and place of birth in order to describe the identity and cultural affiliation of individuals in a population.
Self-reporting ethnicity in an open-ended format (participants write their responses on a black line) is commonly used in many national censuses. Canadian census questions relating to the parent’s ethnicity, race and country of birth include - **Ethnicity**: “What were the ethnic or cultural origins of your child’s ancestors (an ancestor is usually more distant than a grandparent)?” **Race**: “Are biological parent’s of your child (please answer for both parents): White, Chinese, South Asian (e.g. East Indian, Pakistani, Sri Lankan, etc.), Black, Filipino, Latin American, Southeast Asian (e.g. Vietnamese, Cambodian, Malaysian, etc.), Arab, West Asian (e.g. Iranian, Afghan, etc.), Korean, Japanese, Other (please specify) or unknown child is adopted? ” **Country of birth**: “Where were your child’s biological parents born?”

2.2.2.2 Problems with measuring ethnicity

Responses to open-ended questions are impacted by an individual’s understanding of the question and can introduce considerable analytic challenges such as classification error due to non-uniform or non-useful responses (ie. responses for religious affiliation versus geographic and ancestral origins), spelling errors, illegible handwriting and repetition (ie. British and Scottish, two equal geographic ethnicities for the same subject).\textsuperscript{23-27} Analyzing open-ended responses is analytically complex and might not be necessary for capturing finite predetermined geographic ancestral origins.

Statisticians and researchers often rely on categorical variables for analysis, and open-ended ethnicity classifications pose many analytic challenges. These include data cleaning challenges from inconsistent responses, the need to categorize open-ended questions and challenges related to missing data.\textsuperscript{25} Deterministic imputations are often used, where a unique value is assigned to a missing or invalid response through similarities in personal characteristics
or family responses to fill in the missing data (ie. in the case of a child with missing ethnic origin a parent’s response can be used). The 1992 international meeting on the Challenges of Measuring an Ethnic World, recognized the many challenges of measuring ethnicity accurately, yet emphasized the importance of measuring it accurately - “Ethnicity is a fundamental factor in human life: it is a phenomenon inherent in human experience”.

2.2.3 Immigration in Toronto

2.2.3.1 Rates of immigration

Immigration plays an important role in shaping Canada’s population. The 2001 Statistics Canada Census identified that 18% of Canada’s population was born outside of Canada and this number increased to 20%, of the total population in the 2006 census. The increase in immigrants was responsible for 69% of Canada’s population growth between 2001 and 2006. The city of Toronto has a particularly high frequency of immigration. In the 2006 Statistics Canada census, immigration accounted for 46% of Toronto’s population and new immigrants (immigrating between 2001 and 2006) made up 10.8% of the total population. According to a Toronto Public Health survey in 2001, approximately one in ten children younger than 5 years of age living in Toronto were considered landed immigrants.

2.2.3.2 Nutritional concerns of immigrant children

Immigrants to Canada have an increased risk of certain nutrition related concerns including: a higher frequency of food insecurity, higher prevalence of inadequate intake of key nutrients, and higher prevalence of being overweight. Vatanparast et al., using data from CCHS 2.2, suggested that immigrant children have a higher prevalence of inadequate dietary
intake of key nutrients including folate, calcium, zinc and vitamin D. Vogt and Tarasuk in 2007 using data from the CCHS 2.2, suggested that immigrant children between the ages of 6-11 years had higher odds of being overweight than their Canadian born peers.

2.2.4 Dietary acculturation

Food often plays an important role in maintaining or establishing identity when immigrating to a new country. Following immigration, a family may incorporate foods or dietary practices common to their host country, which is known as dietary acculturation. Immigration signifies the physical relocation whereas acculturation represents the social, psychological, and behavioral changes subsequent to that relocation. A number of factors may contribute to the rate of acculturation including having a native born spouse or socializing outside of one’s ethnic group. Potential barriers to dietary acculturation include living in an ethnic enclave, similar ethnic social network, non-fluent English, not employed outside the home and living with older relatives. The consumption of traditional ethnic foods will not necessarily be higher for less acculturated individuals, thus it is inappropriate to assess consumption of traditional foods as a measure of dietary acculturation.

2.2.4.1 Parental influence on children’s eating patterns and habits

Parents have a high degree of control over the dietary experiences of their children and children have the natural tendency to accept the foods offered by their parents. Eating behaviours during the first five years of a child’s life, including what, when and how much to eat, create the foundation for eating patterns later in life and are based on the transmission of cultural and familial beliefs, attitudes, and practices surrounding food and eating.
2.3 Vitamin D deficiency in immigrant populations

Observational epidemiological data suggests that non-western immigrant adults, defined as adults born outside of a western country (Europe, North America, Australia or New Zealand), living in western countries are at increased risk of having 25-hydroxyvitamin D <25 nmol/L.\textsuperscript{99-101} Non-western immigrant pregnant women living in the Netherlands, have a higher prevalence of 25-hydroxyvitamin D <25 nmol/L.\textsuperscript{102} The lower levels of 25-hydroxyvitamin D in non-western immigrants may be due to darker skin pigmentation, tendency to stay out of the sun, clothing coverage and a diet low in fish and dairy products.\textsuperscript{101-106} A study by van der Meer et al. in 2008 found that fatty fish and vitamin D supplements were the greatest contributors to the serum 25-hydroxyvitamin D concentration in non-western immigrant adults living in Netherlands.\textsuperscript{106} A randomized clinical study by Wicherts et al. in 2011, found that vitamin D supplements (daily 800 IU or 100,000 IU/3 months) are more effective for treating vitamin D deficiency in non-western immigrant adults than advised sunlight exposure.\textsuperscript{102}

Children born from immigrant non-western families appear to be at risk of developing vitamin D deficiency rickets.\textsuperscript{62,107-109} Data from the Canadian Paediatric Surveillance Program identified that children whose family immigrated to Canada had a 24% higher odds of developing vitamin D deficiency rickets.\textsuperscript{32} It is not known whether an effect of non-western immigration on 25-hydroxyvitamin D status persists through early childhood and what factors might explain this effect.

2.4 Summary of literature review

Previous studies have suggested that young children born from immigrant non-western families are at increased risk of developing vitamin D deficiency rickets (25-hydroxyvitamin D
<25 nmol/L). However, it is not known whether an effect of non-western immigration on vitamin D status persists through early childhood (i.e. in children older than 1 year of age) and what dietary, environmental or biological determinants of 25-hydroxyvitamin D might explain this effect. We hypothesize that children ages 1-5 years born from non-western immigrant families may be at increased risk of low 25-hydroxyvitamin D concentrations (<50 nmol/L) then western born children, and according to observational epidemiological studies, low levels of 25-hydroxyvitamin D may play a role in common health issues in childhood.

In order to understand the impact of immigration on 25-hydroxyvitamin D concentrations, as a factor independent from ethnicity, we had to ensure that we were measuring geographic ethnicity accurately. Measuring geographic ethnicity is important in vitamin D research due to the impact that latitude and season might have on 25-hydroxyvitamin D concentration. Self-reporting ethnicity in an open-ended format is commonly measured in national censuses including NHANES and CCHS and responses do not always reflect geographic ethnicity. To our knowledge, a geographically based ethnicity question has not been previously developed; thus in this thesis a new standardized geographically based closed-ended ethnicity question was developed and the degree of agreement between the new standardized closed-ended ethnicity question and geographic reclassification of the open-ended ethnicity variables from Statistics Canada standard census was evaluated. Understanding non-western immigration as an exposure is important due to the high frequency of non-western immigration in Canada.
CHAPTER 3 NON-WESTERN IMMIGRANT CHILDREN HAVE LOWER 25-HYDROXYVITAMIN D THAN CHILDREN FROM WESTERN BORN FAMILIES

3.1 Abstract

Objectives: To determine if children ages 1-6 years from non-western immigrant families have lower serum 25-hydroxyvitamin D levels than children from western born families and examine which factors influence this relationship.

Methods: A cross-sectional study of healthy children age 1-6 years recruited through the TARGet Kids! practice based research network. Serum 25-hydroxyvitamin D of non-western immigrants was compared to children from western born families. Children from non-western immigrant families were defined as those who were born, or their parents were born, outside of a western country. Univariate and multiple linear regression were used to identify factors, identified a priori, which might influence this relationship.

Results: 1540 children were included in the analysis. Median age was 36 months, 51% male, 86% ‘light’ skin pigmentation, 55% took vitamin D supplements, mean cow’s milk intake was 1.8 cups/day and 27% were non-western immigrant. Median 25-hydroxyvitamin D was 83 nmol/L with 5% <50 nmol/L. Univariable analysis revealed that non-western immigrant children had 4 nmol/L lower 25-hydroxyvitamin D (p=0.006; 95% CI: 1.3-8.0) and increased odds of 25-hydroxyvitamin D <50 nmol/L (OR 1.9, 95% CI: 1.3–2.9). After adjustment for known vitamin D determinants, the observed difference was attenuated to 0.04 nmol/L (p=0.99, 95% CI: -4.8–4.8) with higher cow’s milk intake (p<0.0001), vitamin D supplementation (p<0.0001), summer season (p=0.008) and increased age (p=0.04) being statistically significant covariates.

Conclusions: There is an association between non-western immigration and lower 25-hydroxyvitamin D in early childhood. This difference appears primarily related to known vitamin D determinants representing opportunities for intervention.
3.2: Background

Vitamin D is an essential micronutrient and plays an important role in bone metabolism and immunological processes.\textsuperscript{110,111} The Institute of Medicine (IOM) and the American Academy of Pediatrics (AAP) suggest that serum 25-hydroxyvitamin D concentration of 50 nmol/L will meet the needs of 97.5\% of the population, for optimal bone related health outcomes.\textsuperscript{7,112} However, there is emerging evidence that serum 25-hydroxyvitamin D levels between 50 and 75 nmol/L are positively associated with a number of chronic health problems later in life.\textsuperscript{113-116} Observational epidemiological studies have suggested that low levels of vitamin D may play a role in fractures\textsuperscript{9,10}, asthma\textsuperscript{11,12}, respiratory infections\textsuperscript{13} and obesity in children.\textsuperscript{14} According to national censes in the United States and Canada approximately 14\% and 42\% of children ages 1-11 years had serum 25-hydroxyvitmain D concentrations <50 nmol/L and between 50-75 nmol/L respectively.\textsuperscript{17,52,117} It is important to identify subgroups of children that are at risk of having low 25-hydroxyvitman D, especially given the possibly long duration of exposure to low 25-hydroxyvitamin D (<50 nmol/L) beginning in childhood.

3.2.1 Rationale

A number of determinants have been identified that affect 25-hydroxyvitamin D in children including skin pigmentation, breastfeeding without vitamin D supplementation, low intake of cow’s milk, higher latitude, and higher adiposity.\textsuperscript{48,55,57,59,67-69,71,118-124} Observational epidemiological data have suggested that non-western adults immigrating to a western country (Europe, North America, Australia or New Zealand) are at increased risk of having 25-hydroxyvitamin D <25 nmol/L.\textsuperscript{99-101} Children under 1 year of age born from immigrant non-western families living in a western country appear to be at risk of developing vitamin D
deficiency rickets. However, it is not known whether an effect of non-western immigration on vitamin D status persists through early childhood (i.e. in children older than 1 year of age) and what dietary, environmental or biological determinants of 25-hydroxyvitamin D might explain this effect.

3.2.2 Hypothesis and objectives

We hypothesized that children older than 1 year from non-western immigrant families in Toronto may be at greater risk of lower serum 25-hydroxyvitamin D concentration compared with children from western born families and this might be explained by known modifiable risk factors for low 25-hydroxyvitamin D, which could be targets for interventions. The primary objective of this study was to determine whether children older than 1 year of age from non-western immigrant families have lower serum 25-hydroxyvitamin D levels than children from western born families. Our secondary objective was to evaluate whether known dietary, environmental or biological determinants of 25-hydroxyvitamin D influence this relationship.

3.3 Methods

This was a prospectively designed cross-sectional observational study of healthy children ages 1 to 6 years in a large urban population.

3.3.1 Participants

Children were recruited between December 2008 and July 2011 during a routine well child doctor’s visit at seven TARGet Kids! participating paediatric and family medicine group practices, representing a diverse sample of children in downtown Toronto (latitude 43.4°N), the
most culturally diverse city in Canada. The TARGet Kids! practice based research network was designed to collect data relevant to nutritional factors and dietary patterns in healthy infants and children. It was developed as a partnership between researchers at the Paediatric Outcomes Research Team (PORT) at the SickKids Research Institute of The Hospital for Sick Children, The Applied Health Research Centre (AHRC) at the Li Ka Shing Knowledge Research Institute of St. Michael’s Hospital, and primary care providers in the Section on Community Paediatrics in the Department of Paediatrics and the Department of Family and Community Medicine at the University of Toronto. Exclusion criteria included any chronic illness (except for asthma), severe developmental delay, non-verbal English, and medications known to affect vitamin D metabolism (ie. anti-seizure medications).

### 3.3.2 Measurements

Survey data were collected through a parent completed standardized data collection form adapted from the Canadian Community Health Survey (CCHS). Trained research assistants embedded in the practices obtained physical measurements, and venous sampling occurred on site at the primary care clinic by a trained phlebotomist. Blood samples were sent daily to the Mount Sinai Services Laboratory in Toronto (www.mountsinaservices.ca).

Our primary exposure variable was non-western immigration determined by the parent(s) and child’s country of birth. Non-western immigration was defined as a child born outside of Europe, North America, Australia or New Zealand or a child who has a parent (one or both) who emigrated from a non-western country. Thus first and second-generation non-western immigrant children were considered non-western immigrants for this analysis because dietary factors affecting young children likely reflect cultural patterns of their parents.
Immigration was measured by the open-ended questions, “where were your child’s biological parents born?” and “where was your child born?”

Our primary outcome, total 25-hydroxyvitamin D, was measured using a competitive two-step chemiluminescence assay (Diasorin LIAISON®). This assay was regularly calibrated according to the internationally recognized ‘Vitamin D External Quality Assessment Scheme’. Extensive testing and validation of this assay has been performed and has demonstrated an intra-assay imprecision of 7.2% at a concentration of 213 nmol/L and an inter-assay imprecision of 4.9% at 32 nmol/L, 8.9% at 77 nmol/L and 17.4% at 213 nmol/L, values which are well within acceptable limits for biochemical measurements.

Our secondary outcome was 25-hydroxyvitamin D <50 nmol/L (binary outcome), based on the IOM reference cut-point.

Clinically relevant covariates that we hypothesized might influence the relationship between non-western immigration and 25-hydroxyvitamin D included ethnicity, sex, age, skin pigmentation, body mass index (BMI), season, current vitamin D supplementation, cow’s milk intake and outdoor play. Ethnicity was captured by the open-ended ethnicity question, “What were the ethnic or cultural origins of your child’s ancestors (an ancestor is usually more distant than a grandparent)?” Two co-authors, Jessica Omand and Sarah Carsley, independently converted responses into the following 5 geographically based ethnic categories: East & Southeast Asian, Southwest Asian, African & Caribbean, mixed western, mixed western/non-western (see chapter 4). Mixed western included children born in families from western countries (eg. Western and Eastern Europe) and mixed western/non-western included children from mixed ethnic families from both non-western countries (eg. East Asian and Latin American) or families from western and non-western countries (eg.
South Asian and Western Europe). Differences in categorization between reviewers were identified less than 5% of the time and subsequently resolved by consensus in each instance. The overall effect of ethnicity was tested using western as the reference of the other 4 geographically based ethnic categories, identified above.

Weight was measured using a precision digital scale (±0.025%; SECA, Germany) and standing height was measured using a stadiometer (SECA, Germany). BMI was calculated as weight in kilograms divided by the height in meters squared.\textsuperscript{136,137} BMI z-scores were calculated using World Health Organization (WHO) growth standards.\textsuperscript{138} Skin pigmentation was measured by trained research assistants using the Fitzpatrick scale, which is a skin pigmentation classification system widely used in dermatological research.\textsuperscript{139-141} Cow’s milk consumption was measured from parental report based on response to the following question, “How many 250 mL cups of cow’s milk does your child drink in a typical day”. All commercially available cow’s milk in Canada is fortified with 100 IU of vitamin D per 250 mL cup.\textsuperscript{142,143} Daily vitamin D supplementation was defined as currently taking a daily multivitamin and/or vitamin D supplement. In Canada, all over the counter multivitamins contain vitamin D and standard dosing of children’s vitamin D containing supplements is 400 IU per dose.\textsuperscript{144} Outdoor play was defined as hours per week spent outside playing, which was used as a proxy for sun exposure.

3.3.3 Statistical Analyses

Descriptive statistics were performed for the primary exposure, outcomes and covariates. For our primary analysis, univariate linear regression was used to determine the unadjusted association between our primary exposure (non-western immigration) and our primary outcome
(25-hydroxyvitamin D as a continuous outcome) and univariate logistic regression was used to determine the unadjusted association between our primary exposure (non-western immigration) and our secondary outcome (25-hydroxyvitamin D < 50 nmol/L as a binary outcome). For our secondary analysis, a multiple linear regression model was developed using our primary outcome (25-hydroxyvitamin D), with adjustment for pre-specified, clinically relevant covariates (described above) to explore factors, which might influence a relationship between non-western immigration and 25-hydroxyvitamin D. All covariates were felt to be clinically important and were included in the final model regardless of p-value.

To explore whether vitamin D supplementation and skin pigmentation may have different effects on 25-hydroxyvitamin D in non-western immigrant children relative to western-born children, two biologically plausible interactions were considered: immigration and skin pigmentation; and immigration and vitamin D supplementation. To achieve a balance between over-fitting and interpretation and limit biases that can result from standard variable selection approaches, these interactions were tested together using a likelihood ratio test. If the p-value for inclusion of the interactions was large (i.e. greater than 0.30), these interactions were considered to be unlikely and were not included in the final models.

Multicollinearity was assessed using the variance inflation factor (VIF), a measure of the degree that a regression coefficient is inflated when other independent variables contain similar information. As the model did not contain large VIF’s (values not exceeding 5) multicollinearity was unlikely to be a problem so each of the hypothesized covariates (including ethnicity and immigration) were considered independent variables. Covariates were identified as confounders of the relationship between non-western immigration and 25-hydroxyvitamin D if they were related both to the exposure (immigrant
status) and the outcome (low vitamin D levels) and changed the parameter estimate for 25-
hydroxyvitamin D by more than 10%.\textsuperscript{147,148}

Data were analyzed using SAS 9.2 for Windows. The study was approved by the
Research Ethics Board of St. Michael’s Hospital and the Hospital for Sick Children, and parents
of all participating children consented to participation in the study.

3.4: Results

In total, consent was secured from parents of 3696 children and 1540 had complete
survey, anthropometric and laboratory data and were included in the analysis (see Figure 2).
Children included and not included in the analysis appeared similar (see Table 2). The median
age of included children was 36 months (SD 18), 51% were male, 86% had ‘light’ skin
pigmentation (Fitzpatrick scale I, II or III), 55% took vitamin D supplements and average cow’s
milk intake was 1.8 cups/day (see Table 2). Children from non-western immigrant families
made up 27% of the population (N=421) (see table 3). Of non-western immigrant families, 4%
(N=18) of children and 96% (N=403) of parents were born outside of Canada, in a non-western
country. Median 25-hydroxyvitamin D was 83 nmol/L and 81 children (5%) had 25-
hydroxyvitamin D levels below 50 nmol/L.

For our primary analysis, univariable linear regression revealed that non-western
immigrant children had lower mean 25-hydroxyvitamin D concentrations than children from
western born families with a difference of 4 nmol/L (85 vs. 89 nmol/L, p=0.006, 95% CI: 1.3 –
8.0). Univariable logistic regression revealed increased odds of 25-hydroxyvitamin D levels less
than 50 nmol/L in non-western immigrant children (OR 1.9, 95% CI: 1.3 – 2.9).
For our secondary analysis, multiple linear regression adjusted for clinically relevant covariates resulted in a reduction of the observed mean 25-hydroxyvitamin D difference between non-western immigrant children and children from western born families to 0.04 nmol/L, which was no longer statistically significant (p=0.99, 95% CI: -4.8 – 4.8) (see table 4).

Covariates which appear to attenuate the relationship between non-western immigration and 25-hydroxyvitamin D included volume of cow’s milk intake (p<0.0001), vitamin D supplementation (p=<0.0001), season (p=0.008) and age (p=0.04) (see table 4). Cow’s milk intake, vitamin D supplementation, season and age were all associated with non-western immigration and had an effect on 25-hydroxyvitamin D. However, only vitamin D supplementation changed the parameter estimate for non-western immigration by more than 10% suggesting it was a confounder. When immigration status and other variables are adjusted for, we did not find that skin pigmentation (p=0.36), ethnicity (p=0.09) or outdoor play (p=0.98) were modifiers of the observed 25-hydroxyvitamin D difference (see table 4).

Interactions between non-western immigration and vitamin D supplementation and non-western immigration and skin pigmentation were tested together which revealed p=0.9, making these interactions unlikely. These interactions were not included in the final model.
Figure 2: Participation flowchart: analysis non-western immigrant children have lower 25-hydroxyvitamin D than children from western born families

- Consent obtained: 3,696
  - Blood obtained: 2081
  - Blood not obtained: 1,615
    - 541 Participants did not have complete data for one or more variables
  - Included in the analysis: 1540
Table 2: Population description for children included and not included in the analysis

<table>
<thead>
<tr>
<th>Child characteristics</th>
<th>Children included in the analysis (N=1540)</th>
<th>Children not included in the analysis (N=1979)*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Frequency (%)</td>
<td>Median (Range)</td>
</tr>
<tr>
<td>Age, months</td>
<td></td>
<td>36 (12–78)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex, male</td>
<td>785 (51)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skin pigmentation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Light</td>
<td>1320 (86)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>zBMI</td>
<td></td>
<td>0.2 (-3.1–3.9)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mixed western</td>
<td>1004 (65)</td>
<td></td>
</tr>
<tr>
<td>Mixed western/non-western</td>
<td>345 (22)</td>
<td></td>
</tr>
<tr>
<td>East Asian &amp; Southeast Asian</td>
<td>90 (6)</td>
<td></td>
</tr>
<tr>
<td>Southwest Asian</td>
<td>70 (5)</td>
<td></td>
</tr>
<tr>
<td>African &amp; Caribbean</td>
<td>31 (2)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Season</td>
<td></td>
<td></td>
</tr>
<tr>
<td>May-Sept (summer)</td>
<td>711 (46)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current cow’s milk intake, 250 mL (1 cup)</td>
<td>2 (0–5)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vitamin D supplements</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>850 (55)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Outdoor Play</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-4 hours/week (0)</td>
<td>629 (41)</td>
<td></td>
</tr>
<tr>
<td>5-7 hours/week (1)</td>
<td>911 (59)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median household income**</td>
<td>56,000</td>
<td>(15,000 – 335,000)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>25-hydroxyvitamin D, nmol/L</td>
<td>83 (11-267)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*2176 subjects were not included in the analysis (1615 blood not obtained and 541 did not have complete survey or anthropometric data). The table above describes 1979 subjects because 197 subjects were removed because they were outliers (15 subjects had zBMI>4, 181 subjects had age <11.5 months or >84 months and 1 subject had 25-hydroxyvitamin D of 352 nmol/L).

** Median household income in Toronto in 2010 was $68,110^{149}
Table 3: Population Description for children from western born families and children from non-western immigrant families

<table>
<thead>
<tr>
<th>Child characteristics</th>
<th>Children from western born families N=1119 (73%)</th>
<th>Children from non-western immigrant families N=421 (27%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, months</td>
<td>36 (12–75)</td>
<td>38 (12–78)</td>
</tr>
<tr>
<td>Sex, male</td>
<td>564 (50)</td>
<td>221 (52)</td>
</tr>
<tr>
<td>Skin pigmentation Light</td>
<td>1061 (95)</td>
<td>259 (62)</td>
</tr>
<tr>
<td>zBMI</td>
<td>0.2 (-3.0–3.8)</td>
<td>0.12 (-3.1–3.9)</td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mixed western</td>
<td>958 (86)</td>
<td>46 (11)</td>
</tr>
<tr>
<td>Mixed western/non-western</td>
<td>143 (13)</td>
<td>202 (48)</td>
</tr>
<tr>
<td>East Asian &amp; Southeast Asian</td>
<td>8 (1)</td>
<td>82 (19)</td>
</tr>
<tr>
<td>Southwest Asian</td>
<td>9 (1)</td>
<td>61 (14)</td>
</tr>
<tr>
<td>African &amp; Caribbean</td>
<td>1 (0.1)</td>
<td>30 (7)</td>
</tr>
<tr>
<td>Season</td>
<td></td>
<td></td>
</tr>
<tr>
<td>May-Sept (summer)</td>
<td>515 (46)</td>
<td>196 (47)</td>
</tr>
<tr>
<td>Current cow’s milk intake, 250 mL (1 cup)</td>
<td>2 (0–5)</td>
<td>500 (0–5)</td>
</tr>
<tr>
<td>Vitamin D supplements</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>633 (57)</td>
<td>217 (52)</td>
</tr>
<tr>
<td>Outdoor Play</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-4 hours/week</td>
<td>399 (36)</td>
<td>230 (55)</td>
</tr>
<tr>
<td>5-7 hours/week</td>
<td>720 (64)</td>
<td>191 (45)</td>
</tr>
<tr>
<td>Median household income</td>
<td>58,000 (15,000–335,000)</td>
<td>50,000 (15,000–269,000)</td>
</tr>
<tr>
<td>25-hydroxvitamin D, nmol/L</td>
<td>84 (12-267)</td>
<td>80 (11-210)</td>
</tr>
</tbody>
</table>
Table 4: Adjusted linear regression model for the association between immigration status and serum 25-hydroxyvitamin D

<table>
<thead>
<tr>
<th>Child characteristics</th>
<th>Difference in serum 25-hydroxyvitamin D (nmol/L)</th>
<th>P-value</th>
<th>R-Squared total=5.2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immigration (non-western:western)</td>
<td>-0.04</td>
<td>0.99</td>
<td></td>
</tr>
<tr>
<td>Age, months</td>
<td>-0.09</td>
<td>0.04*</td>
<td>0.17</td>
</tr>
<tr>
<td>Sex (male:female)</td>
<td>-0.03</td>
<td>0.98</td>
<td>0.00</td>
</tr>
<tr>
<td>Skintype (dark:light)</td>
<td>-2.40</td>
<td>0.37</td>
<td>0.39</td>
</tr>
<tr>
<td>BMI, z-score</td>
<td>-1.01</td>
<td>0.18</td>
<td>0.12</td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mixed western</td>
<td>Reference</td>
<td>0.09**</td>
<td></td>
</tr>
<tr>
<td>East Asian &amp; Southeast Asian</td>
<td>-5.15</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Southwest Asian</td>
<td>-2.44</td>
<td></td>
<td></td>
</tr>
<tr>
<td>African &amp; Caribbean</td>
<td>-14.54</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mixed Western/non-Western</td>
<td>-4.54</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Season (winter:summer)</td>
<td>-4.15</td>
<td>0.008*</td>
<td>0.43</td>
</tr>
<tr>
<td>Daily cow’s milk intake, 250 mL (1 cup)</td>
<td>5.00</td>
<td>&lt;0.0001*</td>
<td>2.58</td>
</tr>
<tr>
<td>Vitamin D supplementation (yes:no)</td>
<td>7.58</td>
<td>&lt;0.0001*</td>
<td>1.36</td>
</tr>
<tr>
<td>Outdoor play (1-4:5-7hrs/week)</td>
<td>0.03</td>
<td>0.99</td>
<td>0.00</td>
</tr>
</tbody>
</table>

* Indicates those variables that are independently associated with serum 25-hydroxyvitamin D (p <0.05)

** The effect of ethnicity in the model was tested using mixed Western as the reference of the other 4 geographically based ethnic categories (East Asian & Southeast Asian, Southwest Asian and African & Caribbean and mixed Western/non-Western.). The p-value represents the overall p-value of all ethnicities tested in the model together.
3.5: Discussion

Immigration is a defining component of urban North America.\cite{150,151} We have identified an association between non-western immigration and lower 25-hydroxyvitamin D in early childhood. Non-western immigrant children having nearly 2-fold increased odds of 25-hydroxyvitamin D less than 50 nmol/L when compared to children from western born families.

When biologically important covariates, related to vitamin D intake and synthesis, were included in our adjusted model, the observed 25-hydroxyvitamin D mean difference between immigration groups could largely be explained by known vitamin D determinants with current vitamin D supplementation having the strongest confounding effect. Cow’s milk intake, season and age were significant covariates in the adjusted linear regression model but did not change the parameter estimate for non-western immigration by more than 10% suggesting they were unlikely to be confounders of the observed association.

Previous studies have identified a number of factors that affect 25-hydroxyvitamin D in children including factors related to cutaneous production of vitamin D such as skin pigmentation (melanin pigment decreases cutaneous synthesis),\cite{59,118,119} ethnicity\cite{104,152} and outdoor time.\cite{153,154} Surprisingly, even though there appeared to be differences in ethnicity, skin pigmentation and outdoor play between non-western immigrant children and children from western born families we did not find that these factors influence the relationship between non-western immigration and 25-hydroxyvitamin D in the adjusted analysis. This could be a consequence of sun avoidance of young children or the relatively low frequency of ‘dark’ skin pigmentation in this population. If skin exposure to the sun were minimal, cutaneous production of 25-hydroxyvitamin D would also be expected to be minimal regardless of skin pigmentation, ethnicity or outdoor playtime.
Strengths of this study were the relatively large sample size with detailed clinical and laboratory data which allowed us to adjust for the many factors known to impact 25-hydroxyvitamin D concentrations in children. Further, our urban population included an ethnically diverse sample from one of the most multicultural cities in the world.

Previous studies have suggested that non-western immigration in children younger than 1 year of age is a risk factor for severe but rare vitamin D deficiency rickets. To our knowledge, the present study is unique in documenting an association between 25-hydroxyvitamin D status and non-western immigration persisting through early childhood, beyond the first year of life. Understanding non-western immigration as an exposure is important due to the high frequency of non-western immigration in much of urban North America. Our finding that vitamin D supplementation appears to be a true confounder of the observed difference in 25-hydroxyvitamin D suggests that vitamin D supplementation may be an excellent target for interventions to increase 25-hydroxyvitamin D among non-western immigrant children.

Limitations of this study include the cross-sectional design, from which causality cannot be inferred. Residual confounding from unknown and unmeasured covariates is also a possibility although such effects are likely to be small given that the adjusted 25-hydroxyvitamin D difference was small. Date since arrival to Canada was not available for this analysis. This may have been beneficial to determine whether a temporal immigration effect impacts 25-hydroxyvitamin D levels. Finally, a language barrier could have precluded some immigrant families from participating in this study. However, only 0.4% of eligible children were actually excluded because of a language barrier yet almost a third of our population were non-western immigrant families.
3.6: Conclusion

Children older than 1 year of age from non-western immigrant families may be at increased risk of lower 25-hydroxyvitamin D. The observed difference appeared confounded by vitamin D supplementation suggesting that targeted interventions to improve vitamin D supplementation among immigrant children beyond the first year of life may be successful at increasing the 25-hydroxyvitamin D status of non-western immigrant children. Non-modifiable factors such as ethnicity and skin pigmentation did not appear to explain the observed difference.
4.1 Abstract

Background: Measuring ethnicity accurately is important for identifying ethnicity variations in disease risk. We have developed a new standardized geographically based closed-ended ethnicity question, which may overcome limitations inherent in existing open-ended ethnicity questions.

Objectives: To evaluate the degree of agreement between a new geographically based closed-ended ethnicity question and a geographically reclassified open-ended variable from Statistics Canada standard census form.

Patients and Methods: A prospectively designed study of respondent agreement. Healthy children age 1-5 years recruited through the TARGet Kids! practice based research network. For the primary analysis, the degree of agreement between geographic reclassification of the Canadian census maternal ethnicity variables and the new geographically based closed-ended maternal ethnicity variable completed by the same respondent and measured at least one year apart was evaluated using a kappa analysis. Trends in reclassification error between open- and closed-ended ethnicity questions were explored.

Results: 862 children who completed TARGet Kids! questionnaires at two time points were included in the analysis. Mean child age was 26 months (range: 12–75 months), 50% of the child subjects were male and median household income was $57,000 (range: 16,000 – 269,000). The kappa agreement statistic for the two definitions of maternal ethnicity was 0.87 (95% CI: 0.84-0.90) indicating good agreement.

Conclusions: The new standardized geographically based closed-ended maternal ethnicity question represents a practical alternative to widely used open-ended ethnicity questions and may improve the accuracy of ethnicity measurement.
4.2: Background

Ethnicity is frequently considered a predictor of health status. Categorizing ethnicity accurately is important for identifying ethnic variations in disease risk. Ethnicity refers to the social group to which an individual belongs and identifies with or is perceived to belong to as a result of shared characteristics including geographic, ancestral origins and cultural commonality (shared beliefs, values and practices). Ethnicity is different from racial classification in that it implies that groups differ by cultural dimensions as well as biological heritage. It has also been suggested that if data are needed on features relating to race (e.g. skin pigmentation), this should be measured directly and separated from the concept of ethnicity.

Measuring ethnicity is hampered by a lack of an internationally recognized method of accurately classifying this concept. Censuses and national surveys, including the Canadian Community Health Survey (CCHS) and United States National Health and Nutrition Examination Survey (NHANES), often collect data on ethnicity, language, religion and place of birth in order to describe the identity and cultural affiliation of individuals in a population. The developers of census instruments try to maintain continuity of the ethnicity measurement over time for comparability purposes. However, as a result of changing immigration patterns, intermarriage and assimilation, definitions of ethnicity are constantly in a state of flux.

Self-reporting ethnicity in an open-ended format is commonly used in national censuses for ethnicity measurement including the Canadian census. However open-ended questions are subject to an individual’s understanding of the question and introduce considerable analytic challenges such as classification error due to non-uniform or non-useful responses (e.g. responses for religious affiliation or Caucasian versus geographic and ancestral origins), spelling errors, illegible handwriting and repetition (i.e. British and Scottish or Argentinian and
Columbian, two equal geographic ethnicities for the same subject). Analyzing open-ended responses is analytically complex and may not be necessary for capturing finite predetermined geographic and ancestral origins. A closed-ended question could offer numerous advantages including easier interpretation and decreased analytic burden.

To overcome these limitations, we have developed a new standardized geographically based closed-ended ethnicity question. The objective of this study was to evaluate the degree of agreement between the new standardized closed-ended ethnicity question and geographic reclassification of the open-ended ethnicity variables from Statistics Canada standard census.

4.3: Methods

This is a prospectively designed study of respondent agreement. Healthy children 1 to 5 years of age were recruited during a routine health maintenance doctor’s visit through the TARGet Kids! primary care practice based research network in Toronto, the most culturally diverse city in Canada, between December 2008 and June 2012. Baseline data collection with completion of the open-ended Canadian census maternal ethnicity questions (initial entry into the TARGet Kids! database and completion of questionnaire before September 2011) and follow-up data collection with completion of the new geographically based closed-ended maternal ethnicity question (follow-up visit with TARGet Kids! and completion of questionnaire after September 2011).
4.3.1 Participants

TARGet Kids! is a collaboration between University of Toronto child health outcomes researchers and primary care physicians from the Department of Paediatrics and the Department of Family and Community Medicine.

Children aged 1 to 5 years were included in this study if they had completed TARGet Kids! questionnaires on two separate occasions at least one year apart by the same respondent. Exclusion criteria for the TARGet Kids! cohort included any chronic illness (except for asthma), non-verbal English, diagnosis of a health condition that affects growth and severe developmental delay and those participants that had incomplete maternal ethnicity data in the baseline or follow-up questionnaires.

4.3.2 Measurements

Trained research assistants administered questionnaires to parents of TARGet Kids! participants at each primary care clinic. The TARGet Kids! Nutrition Health Questionnaire (NHQ) was updated in September 2011, at which point the open-ended Canadian census ethnicity questions were removed from the questionnaire and replaced by the new geographically based closed-ended ethnicity question. Ethnicity was derived from two sources: the open-ended Canadian census ethnicity questions (before September 2011) and the new geographically based closed-ended ethnicity question administered to the same participants at least one year later (after September 2011).
**Figure 3:** Process for reclassification of the open-ended Canadian census maternal ethnicity responses according to the new closed-ended geographically based ethnicity question

**STEP 1**

Response to the question: “Are biological parent’s of your child (please answer for both parents): White, Chinese, South Asian (e.g. East Indian, Pakistani), Sri Lankan, etc.), Black, Filipino, Latin American, Southeast Asian (e.g. Vietnamese, Cambodian, Malaysian, etc.), Arab, West Asian (e.g. Iranian, Afghan, etc.), Korean, Japanese, Other (please specify) or unknown child is adopted?”

If the participant responded:
With a geographical ethnicity (Chinese, South Asian etc.) then transfer data to new classification

If the participant responded:
white or black, move to step 2

**STEP 2**

Response to the question: “What were the ethnic or cultural origins of your child’s ancestors (an ancestor is usually more distant than a grandparent)?”

If the participant responded:
With a geographical ethnicity then transfer data to new classification

If the participant responded:
With a non-uniform or non-useful response (i.e. Canadian, Catholic etc) move to step 3

**STEP 3**

Response to the question: “Where were your child’s biological parents born?”

If the participant responded:
With a country then transfer data to new classification

If the participant responded: White, Canadian and born in Canada then assume western European. Black, Canadian and born in Canada then assume African unknown
For the first ethnicity measurement, we reclassified maternal ethnicity from responses to the open-ended Canadian census questions based on the new closed-ended geographically based ethnicity question. Geographic reclassification of the open-ended questions was based on responses to three Canadian census questions relating to the parent’s ethnicity, race and country of birth. Ethnicity: “What were the ethnic or cultural origins of your child’s ancestors (an ancestor is usually more distant than a grandparent)?” Race: “Are biological parents of your child (please answer for both parents): White, Chinese, South Asian (e.g. East Indian, Pakistani, Sri Lankan, etc.), Black, Filipino, Latin American, Southeast Asian (e.g. Vietnamese, Cambodian, Malaysian, etc.), Arab, West Asian (e.g. Iranian, Afghan, etc.), Korean, Japanese, Other (please specify) or unknown child is adopted?” Country of birth: “Where were your child’s biological parents born?” (see Figure 4). Two co-authors (JO, SC) independently converted responses of these three questions into 19 geographically based ethnic categories: Eastern European, Western European, East Asian (Chinese), East Asian (Korean), East Asian (Japanese), South Asian, Southeast Asian, West Asian, East African, Middle African, Northern African, Southern African, Western African (African sub-categories were based on United Nations geographical divisions156), Latin American, Caribbean Region, Indian-Caribbean, North American Aboriginal, Oceania and Australia or New Zealand.22,135 See figure 3 for the process used to reclassify the open-ended Canadian census maternal ethnicity responses into the new closed-ended geographically based ethnicity categories. JO and SC were blinded to the other classification of the new geographically based closed-ended question and differences in categorization were discussed and resolved by consensus.
Figure 4: Canadian census ethnicity questions\textsuperscript{22} - included on version 1 of TARGet Kids! questionnaire
The second ethnicity measurement was based on parental response to the new geographically based closed-ended maternal ethnicity question (see Figure 5). Research assistants at each TARGet Kids! site were provided with a list of countries that fall under each geographic based ethnicity category to assist parents with categorization (see appendix D). Ethnicity categories were identical for both the first ethnicity measurement (geographically reclassified parental response to open-ended Canadian census ethnicity questions) and the second ethnicity measurement (parental response to the new geographically based closed-ended maternal ethnicity question).

Age, sex and median household income variables were used for baseline comparison. Child’s age was reported in months and sex as male or female. Median household income was calculated using the six-digit postal codes for each participant in order to obtain the median after tax neighborhood household income (using the Statistics Canada Postal Code Conversion File and data from the 2006 Census), which is used as a proxy for individual level household income.
**Figure 5:** New geographically based closed-ended ethnicity question - included on version 2 of TARGet Kids! questionnaire

<table>
<thead>
<tr>
<th>Biological Mother</th>
<th>Biological Father</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eastern European (Polish, Russian, Croatian, etc)</td>
<td>Eastern European (Polish, Russian, Croatian, etc)</td>
</tr>
<tr>
<td>Western European (English, French, Portuguese, etc)</td>
<td>Western European (English, French, Portuguese, etc)</td>
</tr>
<tr>
<td>East Asian (Chinese)</td>
<td>East Asian (Chinese)</td>
</tr>
<tr>
<td>East Asian (Korean)</td>
<td>East Asian (Korean)</td>
</tr>
<tr>
<td>East Asian (Japanese)</td>
<td>East Asian (Japanese)</td>
</tr>
<tr>
<td>South Asian (East Indian, Pakistani, Sri Lankan, etc)</td>
<td>South Asian (East Indian, Pakistani, Sri Lankan, etc)</td>
</tr>
<tr>
<td>Southeast Asian (e.g. Vietnamese, Malaysian, Filipino, etc)</td>
<td>Southeast Asian (e.g. Vietnamese, Malaysian, Filipino, etc)</td>
</tr>
<tr>
<td>West Asian (e.g. Iranian, Afghan, Palestinian, etc)</td>
<td>West Asian (e.g. Iranian, Afghan, Palestinian, etc)</td>
</tr>
<tr>
<td>East African (e.g. Ethiopian, Kenyan, Somali, etc)</td>
<td>East African (e.g. Ethiopian, Kenyan, Somali, etc)</td>
</tr>
<tr>
<td>Middle African (e.g. Cameroonian, Chadian, Congolese, etc)</td>
<td>Middle African (e.g. Cameroonian, Chadian, Congolese, etc)</td>
</tr>
<tr>
<td>Northern African (e.g. Moroccan, Algerian, Egyptian, Sudanese, etc)</td>
<td>Northern African (e.g. Moroccan, Algerian, Egyptian, Sudanese, etc)</td>
</tr>
<tr>
<td>Southern African (e.g. Botswana, South African, etc)</td>
<td>Southern African (e.g. Botswana, South African, etc)</td>
</tr>
<tr>
<td>Western African (e.g. Ghanaian, Nigerian, Guinean, etc)</td>
<td>Western African (e.g. Ghanaian, Nigerian, Guinean, etc)</td>
</tr>
<tr>
<td>Latin American (e.g. Argentinean, Costa Rican, Mexican, etc)</td>
<td>Latin American (e.g. Argentinean, Costa Rican, Mexican, etc)</td>
</tr>
<tr>
<td>Caribbean Region (e.g. Jamaican, Trinidadian/Tobagonian, etc)</td>
<td>Caribbean Region (e.g. Jamaican, Trinidadian/Tobagonian, etc)</td>
</tr>
<tr>
<td>Indian-Caribbean (e.g. Guyana with origins in India)</td>
<td>Indian-Caribbean (e.g. Guyana with origins in India)</td>
</tr>
<tr>
<td>North American Aboriginal (Inuit, Métis, First Nations, etc)</td>
<td>North American Aboriginal (Inuit, Métis, First Nations, etc)</td>
</tr>
<tr>
<td>Oceania (e.g. Samoan, Fijian, etc)</td>
<td>Oceania (e.g. Samoan, Fijian, etc)</td>
</tr>
<tr>
<td>Australian or New Zealander</td>
<td>Australian or New Zealander</td>
</tr>
</tbody>
</table>

- Unknown: Child is adopted
4.3.3 Statistical Analysis

Descriptive statistics including age, sex and median household income were performed on a convenience sample of children. Frequency distributions based on the geographic reclassification of the Canadian census open-ended maternal ethnicity variables and the new geographically based closed-ended maternal ethnicity variables were generated. The number of subjects who identified with non-useful responses (non geographic and ancestral origins) from the Canadian census ethnicity questions were identified. To determine the degree of agreement between geographic reclassification of the Canadian census maternal ethnicity variables and the new geographically based closed-ended maternal ethnicity variable a kappa analysis was performed. A Kappa reflects the degree of agreement between the ethnicity variables, while removing the effect of random agreement due to chance.\textsuperscript{159,160} Kappa values lower then 0.4 have a low degree of agreement, values between 0.4 and 0.75 have a fair to good level of agreement and levels above 0.75 are considered to have a high level of agreement.\textsuperscript{161,162} The overall accuracy is a global measure of classification accuracy and represents the percent of individuals that were classified correctly.\textsuperscript{163} Overall accuracy is calculated by summing the number of subjects classified correctly for each ethnicity category, and dividing this by the total number of subjects included in the analysis.\textsuperscript{163} The sensitivity and specificity of the maternal ethnicity questions were calculated using responses to the new geographically based closed-ended maternal ethnicity variable as the reference. Sensitivity measures the ability of our geographic reclassification of the Canadian census maternal ethnicity question to correctly classify an individual with the same ethnicity, when the same participant completes the new geographically based closed-ended maternal ethnicity question (ie. Western European in both circumstances, when the individual is Western European).\textsuperscript{164} Specificity measures the ability of our geographic
reclassification of the Canadian census maternal ethnicity question to correctly classify an individual as not identifying with a certain ethnicity according to the closed-ended maternal ethnicity question. Systematic trends in reclassification error (≥ 10% misclassification) were explored.

Data was analyzed using SAS 9.3 for Windows. The study was approved by the Research Ethics Board of St. Michael’s Hospital and the Hospital for Sick Children, and all parents/guardians of participating children consented to be in the study.

4.4 RESULTS

4.4.1 Study Population

Of the 1099 children who participated in TARGet Kids! at baseline and follow-up, 862 children had responses to both the Canadian census open-ended maternal ethnicity questions and the new geographically based closed-ended maternal ethnicity question and were included in the analysis (see Figure 6). Mean age at baseline was 26 months (range: 12-75 months), 50% of the child subjects were male and median household income was $57,000 (range: 16,000 – 269,000) (see table 5). The median household income in Toronto in 2010 was $68,110. In the reclassification of the Canadian census open-ended maternal ethnicity questions, many participants identified their ethnicity as Canadian (N=746), Caucasian (N=82) or a religious affiliation (N=275) and 541 subjects identified as a ‘White, Canadians, and born in Canada’.
Figure 6: Participation flowchart: analysis measuring ethnicity in children: a geographic approach
Table 5: Baseline demographics for children included in the analysis and children not included in the analysis, measuring ethnicity in children: a geographic approach

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Participants included in the analysis N = 862</th>
<th>Participants not included in the analysis N = 3458</th>
</tr>
</thead>
<tbody>
<tr>
<td>Child’s age (months)*</td>
<td>Median (CI) or N (%)</td>
<td>Median (CI) or N (%)</td>
</tr>
<tr>
<td></td>
<td>26 (12 - 75)</td>
<td>35 (12-80)</td>
</tr>
<tr>
<td>Sex (males)**</td>
<td>426 (50%)</td>
<td>1389 (52%)</td>
</tr>
<tr>
<td>Median household income ($)***</td>
<td>57,000 (16,000–269,000)</td>
<td>56,000 (15,000 – 335,000)</td>
</tr>
<tr>
<td>Maternal Ethnicity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eastern European</td>
<td>99 (11%)</td>
<td>402 (13%)</td>
</tr>
<tr>
<td>Western European</td>
<td>569 (66%)</td>
<td>1889 (62%)</td>
</tr>
<tr>
<td>East Asian (Chinese)</td>
<td>47 (5%)</td>
<td>157 (5%)</td>
</tr>
<tr>
<td>East Asian (Korean)</td>
<td>11 (1%)</td>
<td>34 (1%)</td>
</tr>
<tr>
<td>East Asian (Japanese)</td>
<td>12 (1%)</td>
<td>40 (1%)</td>
</tr>
<tr>
<td>South Asian</td>
<td>41 (5%)</td>
<td>159 (5%)</td>
</tr>
<tr>
<td>Southeast Asian</td>
<td>40 (5%)</td>
<td>139 (5%)</td>
</tr>
<tr>
<td>West Asian</td>
<td>6 (1%)</td>
<td>34 (1%)</td>
</tr>
<tr>
<td>East African</td>
<td>2 (0.2%)</td>
<td>20 (0.6%)</td>
</tr>
<tr>
<td>Middle African</td>
<td>0</td>
<td>2 (0.07%)</td>
</tr>
<tr>
<td>Northern African</td>
<td>0</td>
<td>1 (0.03%)</td>
</tr>
<tr>
<td>Southern African</td>
<td>0</td>
<td>7 (0.2%)</td>
</tr>
<tr>
<td>Western African</td>
<td>0</td>
<td>4 (0.1%)</td>
</tr>
<tr>
<td>Latin American</td>
<td>26 (3%)</td>
<td>112 (4%)</td>
</tr>
<tr>
<td>Caribbean Region</td>
<td>7 (1%)</td>
<td>51 (2%)</td>
</tr>
<tr>
<td>Indian-Caribbean</td>
<td>1 (0.1%)</td>
<td>9 (0.3%)</td>
</tr>
<tr>
<td>North American Aboriginal</td>
<td>1 (0.1%)</td>
<td>1 (0.03%)</td>
</tr>
<tr>
<td>Oceania</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Australian or New Zealander</td>
<td>0</td>
<td>2 (0.07%)</td>
</tr>
</tbody>
</table>
4.4.2 Agreement between measures of ethnicity

The frequency distribution of subject’s maternal ethnicity by geographically reclassified Canadian census variables and the new geographically based closed-ended maternal ethnicity variable are outlined in table 6.

The kappa for the agreement between the two maternal ethnicity variables was 0.87 (95% CI: 0.84-0.90) indicating good agreement (see table 7 for the kappa matrix). The overall accuracy, for all ethnicity categories was 93%. The sensitivity and specificity of the maternal ethnicity questions ranged from 83-100% and 96-100% respectively (see table 6).

Table 6: Frequency of maternal ethnicity based on the geographically reclassified open-ended Canadian census variable and the new geographically based closed-ended variable as well as sensitivity and specificity of the two measures of ethnicity

<table>
<thead>
<tr>
<th>Maternal Ethnicity</th>
<th>Geographically reclassified Canadian census variable N = 862</th>
<th>New geographically based closed-ended variable N = 862</th>
<th>Sensitivity (true positive) / (true positive + false negative)*</th>
<th>Specificity (true negative) / (true negative + false positive)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eastern European</td>
<td>99 (11%)</td>
<td>125 (15%)</td>
<td>93 (87-98)</td>
<td>96 (94-97)</td>
</tr>
<tr>
<td>Western European</td>
<td>569 (66%)</td>
<td>539 (62%)</td>
<td>94 (91-95)</td>
<td>96 (94-98)</td>
</tr>
<tr>
<td>East Asian (Chinese)</td>
<td>47 (5%)</td>
<td>48 (6%)</td>
<td>96 (84-99)</td>
<td>99.6 (98.8-99.9)</td>
</tr>
<tr>
<td>East Asian (Korean)</td>
<td>11 (1%)</td>
<td>13 (2%)</td>
<td>100 (68-100)</td>
<td>99.8 (99.1-99.9)</td>
</tr>
<tr>
<td>East Asian (Japanese)</td>
<td>12 (1%)</td>
<td>11 (1%)</td>
<td>92 (60-99.6)</td>
<td>100 (99-100)</td>
</tr>
<tr>
<td>South Asian</td>
<td>41 (5%)</td>
<td>42 (5%)</td>
<td>95 (82-99)</td>
<td>99.6 (98.8-99.9)</td>
</tr>
<tr>
<td>Southeast Asian</td>
<td>40 (5%)</td>
<td>33 (4%)</td>
<td>83 (67-92)</td>
<td>100 (99-100)</td>
</tr>
<tr>
<td>Latin American</td>
<td>26 (3%)</td>
<td>28 (3%)</td>
<td>92 (73-99)</td>
<td>99.5 (99.7-99.8)</td>
</tr>
</tbody>
</table>

* The results should be interpreted with caution as some ethnicity categories have small sample sizes
** Ethnicity categories with subject sizes less than 10 were excluded (West Asian N=6, East African N=2, Caribbean Region N=7, Indian-Caribbean N=1, North American Aboriginal N=1, and ethnicity categories with N=0 include Middle African, Northern African, Southern African, Western African, Oceania, and Australia or New Zealander)
Table 7: Cross-Tabulation of open-ended ethnicity questions from the Canadian census and the new standardized closed-ended question

<p>| Reclassified open-ended ethnicity questions from the Canadian census | Eastern European | Western European | East Asian Chinese | East Asian Korean | East Asian Japanese | South Asian | Southeast Asian | West Asian | African | Latin American | Caribbean Region | Indian-Caribbean | North American Aboriginal | Oceania | Australian or New Zealander | Total |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Eastern European | 93 | 31 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 125 |
| Western European | 4 | 530 | 2 | 0 | 0 | 0 | 1 | 0 | 0 | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 539 |
| East Asian | 0 | 1 | 45 | 0 | 0 | 0 | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 48 |
| East Asian | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 11 |
| South Asian | 0 | 0 | 0 | 0 | 0 | 0 | 39 | 3 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 42 |
| Southeast Asian | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 33 |</p>
<table>
<thead>
<tr>
<th></th>
<th>Eastern European</th>
<th>Western European</th>
<th>East Asian Chinese</th>
<th>East Asian Korean</th>
<th>East Asian Japanese</th>
<th>South Asian</th>
<th>Southeast Asian</th>
<th>West Asian</th>
<th>African</th>
<th>Latin American</th>
<th>Caribbean Region</th>
<th>Indian-Caribbean</th>
<th>North American Aboriginal</th>
<th>Oceania</th>
<th>Australian or New Zealander</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>West Asian</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>6</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>9</td>
</tr>
<tr>
<td>African</td>
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<td>0</td>
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<td>0</td>
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<td>Latin American</td>
<td>0</td>
<td>4</td>
<td>0</td>
<td>0</td>
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<td>24</td>
<td>0</td>
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<td>0</td>
<td>0</td>
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<td>0</td>
<td>28</td>
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<tr>
<td>Caribbean Region</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>6</td>
<td>1</td>
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<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>8</td>
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<tr>
<td>Indian-Caribbean</td>
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<td>Oceania</td>
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<td>0</td>
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<td>0</td>
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</tr>
<tr>
<td>Australian or New Zealander</td>
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<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
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<td>0</td>
<td>0</td>
<td>0</td>
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</tr>
<tr>
<td>Total</td>
<td>99</td>
<td>569</td>
<td>47</td>
<td>11</td>
<td>12</td>
<td>41</td>
<td>40</td>
<td>6</td>
<td>2</td>
<td>26</td>
<td>7</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>862</td>
</tr>
</tbody>
</table>
4.4.3 Trends in reclassification error

In exploring trends in reclassification error of the Canadian census open-ended ethnicity questions, we divided the number of subjects classified incorrectly using the open-ended ethnicity questions by the number of subjects with the new geographically based closed ended ethnicity variable, as the reference. We incorrectly classified Eastern European as Western European 25% of the time (N=31/125), West Asian as Eastern European 22% (N=2/9), West Asian as South Asian 11% (N=1/9), Latin American as Western European 14% (N=4/28), Caribbean Region as Indian-Caribbean 12% (N=1/8), Indian-Caribbean as Caribbean 100% (N=1/1) and North American Aboriginal as Western European 67% (N=2/3).

4.5 DISCUSSION

Classifying ethnicity is important for describing ethnicity variation in disease risk of populations. Governments and private organizations have used a number of different classifications of ethnicity. To our knowledge, a geographically based closed-ended ethnicity question has not been developed. We developed a new standardized closed-ended geographically based ethnicity question to overcome many of the barriers inherent in open-ended ethnicity questions. In this study, we have evaluated the degree of agreement between the new standardized closed-ended ethnicity question and geographic reclassification of the open-ended ethnicity variables from Canadian census. The new standardized closed-ended ethnicity responses were in good agreement with geographic reclassification of ethnicity from existing open-ended Canadian census questions, with a Kappa statistic of 0.87.
Our results suggest that the open-ended Canadian census questions can be converted to the new standardized closed-ended geographically based ethnicity question. This may facilitate harmonizing responses from open-ended Statistics Canada ethnicity questions with the new standardized closed ended question allowing for consistency of measurement over time. Further the two ethnicity measures were in good agreement, suggesting that the new standardized closed-ended geographically based ethnicity question may measure ethnicity as good as or better than the commonly used open-ended Canadian census question.

Capturing ethnicity from open-ended questions has the advantage of allowing participants to self-define their ethnicity without pre-defined categories. However, if the respondent does not understand the meaning of the question this can lead to arbitrary responses. A closed-ended question, on the other hand, is more objective and it limits the respondent to answer based on pre-defined geographic ancestry categories. Our new standardized geographically based closed-ended ethnicity question offers a number of advantages including easier interpretation and ease of use in statistical analysis.

In our study, the most common problems with reclassifying ethnicity from open-ended questions resulted from non-uniform or non-useful open-ended responses and errors resulting from participant misinterpretation of the open-ended question. For example, many participants identified ethnicity as Canadian, Caucasian or as a religious affiliation. To geographically reclassify the open-ended questions we made the assumption that ‘White, Canadian and born in Canada’ are individuals of Western European ancestry. However, such assumptions may have led to reclassification error which may explain why Eastern European was incorrectly classified as Western European based on open-ended questions 25% of the time. Such errors based on reclassification of open-ended questions may not have occurred if the question had been closed-
ended and without the option of ‘Canadian’ as a response. A challenge related to measuring ethnicity by a closed-ended question is that individuals may not know the geographical origin of their ancestors. However, a participant who is unaware of their ancestral origins would respond inaccurately to a question regarding the ancestral geographic origins regardless of the question format.

Limitations

This study has several limitations. The large number of subjects with Eastern and Western European ancestry in our population resulted in less power to detect reclassification error of the open-ended questions in individuals with African, Caribbean, and Aboriginal ancestry. A language barrier could have precluded some families from participating in this study. However, only 0.4% of eligible children were actually excluded because of language barrier.

Although open- and closed-ended responses were separated in time by at least one year to minimize recall of previous responses (the first response is unlikely to influence the second), it is possible that individuals may perceive their ethnicity differently over time due to a change in immigration status, nationality, intermarriage or assimilation, but a question regarding geographical origin of their ancestors should not change. Additionally, participants included in this study had completed TARGet Kids! questionnaires on two occasions which may represent a motivated population of individuals who may be more aware of their ancestry. Although the standardized closed ended question offers many analytic advantages over open-ended questions, it may take respondents longer to complete the closed ended question, which we were not able to evaluate in this study. Finally, although multiple ethnicity responses were allowed with both open- and closed-ended questions, these individuals, representing 18% of mothers, were
excluded from our analysis. Future research is needed to determine the level of agreement between open- and closed-ended ethnicity questions among individuals with multiple ancestral ethnicities.

4.6 CONCLUSION

The new standardized geographically based closed-ended maternal ethnicity question represents a practical alternative to widely used open-ended ethnicity questions. Reclassification of open-ended ethnicity questions from the Canadian census resulted in good agreement with the new standardized closed-ended question. Further, the new standardized closed-ended ethnicity question may improve the accuracy for which ethnicity is measured. The method of reclassifying ethnicity outlined in this study could be applied to Canadian census data. The new standardized closed-ended ethnicity question is simpler to use in analysis and may lead to improved interpretation of ethnicity by respondents.
CHAPTER 5 OVERALL DISCUSSION

An association between non-western immigration and lower 25-hydroxyvitamin D in early childhood was identified, with non-western immigrant children having nearly 2-fold increased odds of 25-hydroxyvitamin D less than 50 nmol/L. This difference appears primarily related to known vitamin D determinants representing opportunities for intervention.

A new standardized closed-ended geographically based ethnicity question was developed to overcome many of the barriers inherent in open-ended ethnicity questions and the degree of agreement between the new standardized closed-ended ethnicity question and geographic reclassification of the open-ended ethnicity variables from Canadian census was evaluated.

In this thesis I have tested an a priori generated hypothesis and have worked through a pre-specified data analysis plan (see appendix E) which I created with support from my mentors. In epidemiologic research, it is important to a priori develop hypotheses and test these hypotheses following strict pre-specified primary and secondary objectives, in order to maintain the statistical integrity of a p-value of less than 0.05.165

STUDY 1 NON-WESTERN IMMIGRANT CHILDREN HAVE LOWER 25-HYDROXYVITAMIN D THAN CHILDREN FROM WESTERN BORN FAMILIES

I, and others, have hypothesized that non-western immigration may be a determinant of 25-hydroxyvitamin D status.62,107,108 The aim of my first study was to determine whether an effect of non-western immigration on vitamin D status persists through early childhood and if an effect of immigration persists, is this due to known determinants of 25-hydroxyvitamin D or is it a new independent effect.
We identified an association between non-western immigration and lower 25-hydroxyvitamin D in early childhood with non-western immigrant children having nearly 2-fold increased odds of 25-hydroxyvitamin D less than 50 nmol/L when compared to children from western born families. The observed 25-hydroxyvitamin D mean difference between immigration groups could largely be explained by known vitamin D determinants with current vitamin D supplementation having the strongest confounding effect. There appeared to be differences in ethnicity, skin pigmentation and outdoor play between non-western immigrant children and children from western born families according to the baseline demographics; however, we did not find that these factors influenced the relationship between non-western immigration and 25-hydroxyvitamin D in the adjusted analysis.

In this study, 55% of children took a supplement containing vitamin D. According to the Canadian CCHS 2.2 data (2004), 40% of children age 1 to 8 years took supplements; 35% and 41% of children ages 1-3 and 4-8 respectively took a supplement containing vitamin D. According to the United States NHANES 1999-2004, 43.1% and 37.4% of children age 2-4 and 5-11 years took a dietary supplement respectively. The higher frequency of vitamin D supplement use in this study (55%) may reflect the increased awareness (due to laboratory measure of 25-hydroxyvitamin D) of physicians at the TARGet Kids! practicing clinics, and thus increased recommendations to supplement children with vitamin D or parents may be more interested in health interventions.

One interpretation of my results could be the inverse supplement hypothesis. This hypothesis states that people at risk of nutrient inadequacy are often not the ones who take dietary supplements. The inverse supplement hypothesis is supported by data in the CCHS and NHANES. A number of epidemiologic studies have found a positive association
between income and supplement use\textsuperscript{166,146,169,170} and higher level of education and supplement use in adults and children.\textsuperscript{166,168,171} According to statistics Canada 2007, immigrants tend to have a lower social economic status (SES) compared with their Canadian born equals.\textsuperscript{172} Our data suggest that non-western immigrant families and western families had similar median household incomes (see table 3). The median household income of our population was $56,000 and the median household income in Toronto in 2010 was $68,110.\textsuperscript{149} It may be hypothesized that the difference in vitamin D supplement use may be accounted for by differences in household income; however, the median household income in our population appears quite similar at $57,000 between children taking and not taking supplements, (see appendix F).

The eating behaviours of children during the first five years create the foundation for eating patterns later in life and are based on cultural and family beliefs, attitudes, and practices surrounding food and eating.\textsuperscript{93,98} For this reason, first and second-generation non-western immigrant children were considered non-western immigrants for this analysis.

It would have been beneficial to incorporate time since immigration into the analysis in order to account for differential dietary acculturation; however this data was not available to us. Thus, we cannot make any inferences on the effect of acculturation on the observed 25-hydroxyvitamin D difference. Future studies on immigration and nutrition could assess dietary acculturation by capturing data on time since immigration and including it in the statistical models. This may be important when developing nutrition education or interventions.\textsuperscript{92} According to a study by Hamner et al. in 2012, found that folic acid supplement use is more common amongst non-Hispanic white women than Hispanic American or non-Hispanic black women and frequency of folic acid supplementation increased as time since immigration increased.\textsuperscript{173}
To explore whether the effect of vitamin D supplementation (yes or no) or skin pigmentation (light or dark) on 25-hydroxyvitamin D was different between western and non-western immigrant children, we tested the interaction between vitamin D supplementation and non-western immigration as well as between skin pigmentation and non-western immigration together. Interaction effects represent the combined effects of two variables on the dependent measure (25-hydroxyvitamin D). Using a likelihood ratio test, the joint p-value for these interactions was 0.9 suggesting that neither interaction was likely. An alternative approach to exploring these issues would have been to stratify the population by supplement users and non-supplement users as well as by light and dark skin pigmentation and repeat our primary and secondary analyses. We chose to use the interaction approach to: 1) limit multiple hypothesis testing 2) maximize statistical power by using all of our data and 3) stratification cannot differentiate whether observed differences between stratum are statistically different from each other.

I chose to include a categorical ethnicity variable with 5 categories (mixed Western, East Asian & Southeast Asian, Southwest Asian, African & Caribbean and mixed Western/non-Western) in my primary model. Categorical variables used in a regression model are coded as dummy variables; however, the problem with dummy variables arising from a categorical variable is that they are not independent variables. Thus, we are not able to interpret the p-value of each ethnicity category. We are able to interpret the coefficients of the different ethnicity categories, as they tell us how the intercept changes compared to the reference (mixed Western) and the overall p-value, which identifies whether any of the ethnicity categories (all together) are different from the reference.
An example of an intervention targeting an immigrant population is folic acid fortification of masa flour. The Food and Drug Associations (FDA) mandated fortification of enriched cereal grains (ie. white flour) in 1998. However, corn masa flour (used to make corn tortillas or tamales; a common staple in a traditional Hispanic diet), has not been approved for the addition of folic acid. Folic acid fortification of enriched grains has been a successful public health strategy, and significantly reduced the number of neural tube defects (NTD), by nearly 2/3 since fortification. Hispanic women are less likely to consume a supplement containing folic acid and are 20% more likely to have a child with a NTD; thus, an argument to fortify a staple food in a traditional Hispanic diet has been made. It has been hypothesized that fortification of corn masa flour in the United States would increase total dietary folic acid in Hispanic women by approximately 20%, according to data from NHANES.

Strengths of this study were the relatively large sample size with detailed clinical and laboratory data which allowed us to adjust for the many factors known to impact 25-hydroxyvitamin D concentrations in children. Further, our urban population included an ethnically diverse sample from one of the most multicultural cities in the world.

Previous studies have suggested that non-western immigration in children younger than 1 year of age is a risk factor for severe but rare vitamin D deficiency rickets. To our knowledge, the present study is unique in documenting an association between 25-hydroxyvitamin D status and non-western immigration persisting through early childhood, beyond the first year of life. Understanding non-western immigration as an exposure is important due to the high frequency of non-western immigration in much of urban North America and the health outcomes related to 25-hydroxyvitmain D levels. Our finding that
vitamin D supplementation appears to be a true confounder of the observed difference in 25-hydroxyvitamin D suggests that vitamin D supplementation may be an excellent target for interventions to increase 25-hydroxyvitamin D among non-western immigrant children.

Limitations of this study include the cross-sectional design, from which causality cannot be inferred. Residual confounding from unknown and unmeasured covariates is also a possibility although such effects are likely to be small given that the adjusted 25-hydroxyvitamin D difference was small. Finally, a language barrier could have precluded some immigrant families from participating in this study. However, only 0.4% of eligible children were actually excluded because of a language barrier yet almost a third of our population were non-western immigrant families.

**STUDY 2: MEASURING ETHNICITY IN CHILDREN: A GEOGRAPHIC APPROACH**

Classifying ethnicity is important for describing ethnicity variation in disease risk of populations. We have developed a new standardized closed-ended geographically based ethnicity question to overcome many of the barriers inherent in open-ended ethnicity questions. In this study, we have evaluated the degree of agreement between the new standardized closed-ended ethnicity question and geographic reclassification of the open-ended ethnicity variables from Canadian census. The new standardized closed-ended ethnicity responses were in good agreement with geographic reclassification of ethnicity from existing open-ended Canadian census questions, with a Kappa statistic of 0.87.

Our results have suggested that the open-ended Canadian census questions can be converted to the new standardized closed-ended geographically based ethnicity question. This may facilitate harmonizing responses from open-ended Statistics Canada ethnicity questions.
with the new standardized closed-ended question allowing for consistency of measurement over time. Further, the two ethnicity measures were in good agreement, suggesting that the new standardized closed-ended geographically based ethnicity question may measure ethnicity as well as or better than the commonly used open-ended Canadian census question.

Capturing ethnicity from open-ended questions has the advantage of allowing participants to self-define their ethnicity without pre-defined categories. However, if the respondent does not understand the meaning of the question this can lead to arbitrary responses. A closed-ended question, on the other hand, is more objective and it limits the respondent to answer based on pre-defined geographic ancestry categories. Our new standardized geographically based closed-ended ethnicity question offers a number of advantages including easier interpretation and ease of use in statistical analysis.

In our study, the most common problems with reclassifying ethnicity from open-ended questions resulted from non-uniform or non-useful open-ended responses and errors resulting from participant misinterpretation of the open-ended question. For example, many participants identified ethnicity as Canadian, Caucasian or as a religious affiliation. To geographically reclassify the open-ended questions we made the assumption that ‘White, Canadian and born in Canada’ are individuals of Western European ancestry. However, such assumptions may have led to reclassification error which may explain why Eastern European was incorrectly classified as Western European based on open-ended questions 25% of the time. Such errors based on reclassification of open-ended questions may not have occurred if the question had been closed-ended and without the option of ‘Canadian’ as a response. A challenge related to measuring ethnicity by a closed-ended question is that individuals may not know the geographical origin of their ancestors. However, a participant who is unaware of their
ancestral origins would respond inaccurately to a question regarding the ancestral geographic origins regardless of the question format.

This study has several limitations. The large number of subjects with Eastern and Western European ancestry in our population resulted in less power to detect reclassification error of the open-ended questions in individuals with African, Caribbean, and Aboriginal ancestry. A language barrier could have precluded some families from participating in this study. However, only 0.4% of eligible children were actually excluded because of language barrier.

Although open- and closed-ended responses were separated in time to minimize recall of previous responses (the first response is unlikely to influence the second), it is possible that individuals may perceive their ethnicity differently over time due to a change in immigration status, nationality, intermarriage or assimilation, but a question regarding geographical origin of their ancestors should not change. Additionally, participants included in this study had completed TARGet Kids! questionnaires on two occasions which may represent a motivated population of individuals who may be more aware of their ancestry. Although the standardized closed-ended question offers many analytic advantages over open-ended questions, it may take respondents longer to complete the closed-ended question, which we were not able to evaluate in this study. Finally, although multiple ethnicity responses were allowed with both open- and closed-ended questions, these individuals, representing 18% of mothers, were excluded from our analysis. Future research is needed to determine the level of agreement between open- and closed-ended ethnicity questions among individuals with multiple ancestral ethnicities.
CHAPTER 6 CONCLUSIONS AND FUTURE DIRECTIONS

We have identified that children age 1-6 years enrolled in TARGGet Kids! who are living in Toronto from non-western immigrant families had lower 25-hydroxyvitamin D concentrations than children from western born families. We also have identified that vitamin D supplementation appeared to be a true confounder of the observed difference and that ethnicity and skin pigmentation were non-modifiable factors which did not explain the observed difference. Cow’s milk intake, season and age were significant covariates in the adjusted linear regression model but were not considered confounders. We concluded that targeted interventions aimed at improving vitamin D supplementation among immigrant children 1-6 years of age might be successful at increasing the 25-hydroxyvitamin D status of this population (ie. increased awareness of clinicians who see families that immigrated to Western country). This information contributed to a better understanding of the vitamin D status of young immigrant children and may have important implications for parents, dietetic practice and health policy makers.

Through the process of conducting this project there was a need to reclassify the open-ended Canadian Census ethnicity variable into a categorical variable to adjust for ethnicity. Ethnicity was categorized based on geographic ancestral origin, rather than multiple layers including race, ethnicity, nationality, and/or religion. We identified that prospective collection of the new geographically based closed-ended maternal ethnicity question was in good agreement with the retrospective geographic reclassification of the open-ended Canadian census ethnicity questions. We were then able to adjust for ethnicity in the model using the new geographically reclassified maternal ethnicity variable and determine whether exposure to non-western immigration is related to 25-hydroxyvitamin D serum concentration.
Future research is needed to better understand the effect of duration since immigration on a child’s 25-hydroxyvitamin D status. Thus, our future plan is to investigate whether the number of years that a family has lived in Canada is related to a child’s vitamin D status. Future research is needed on the impact of 25-hydroxyvitamin D status during early childhood on health outcomes during adolescents and adult life.

The TARGet Kids! research team plans to expand the number of participating clinics and hopefully increase representation of all ethnic groups living in Toronto. Finally, given that dietary intake is likely an important predictor of 25-hydroxyvitamin D status in this population, it is important that vitamin D dietary intake in TARGet Kids! is accurately measured. Validation of TARGet Kids! dietary intake measurements based on a gold standard such as an estimated food record is an important next step.
CHAPTER 7 REFERENCES


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CHAPTER 8 APPENDICES APPENDIX A – CONSENT FORM
PARENT/GUARDIAN LETTER OF INFORMATION and CONSENT FORM
(for participants 1-5 years)

Study Title: TARGet Kids! Measuring nutrition in young preschool-aged children in the primary care practice setting

Principal Investigator at St. Michael's Hospital:
Dr. Jonathon Maguire, Department of Pediatrics, St. Michael's Hospital
Telephone# (416) 813-2129 (available Mon – Friday 9am to 5pm)

Overall Study Principal Investigator:
Dr. Patricia Parkin, Division of Paediatric Medicine, The Hospital for Sick Children
Telephone# (416) 813-6933 (available Mon – Friday 9am to 5pm)

Co-investigators:
Dr. Catherine Birken, Division of Paediatric Medicine, The Hospital for Sick Children
Telephone# (416) 813-6933 (available Mon – Friday 9am to 5pm)
Dr. Brian McCrindle, Heart Centre, the Hospital for Sick Children
Telephone# (416) 813-3527

Study Coordinator
Marina Khovratovich, Division of Paediatric Medicine, The Hospital for Sick Children
Telephone# (416) 813-2129 (available Mon-Friday 9am to 5pm)

Funding:
Funding for the TARGet Kids study is provided by The Hospital for Sick Children Foundation’s grant to our research program, the Pediatric Outcomes Research Team (PORT) and the Canadian Institute for Health Research (CIHR).

Before you decide whether or not your child will take part, it is important that you read and understand this research consent form. This form provides all the information we think you will need to know in order to decide whether or not you wish to have your child take part in this study. You must be sure to understand the possible benefits and risks in order to make an informed decision. If you wish, please discuss it with family members, friends, the study physician, your child’s treating physician or your family physician. If, after reading this document, there is anything you do not understand about this study, please ask the study physician or the study personnel. If all your questions are answered to your satisfaction and you decide to have your child take part, you will be asked to sign this consent document. You should not sign this form until you are sure you understand everything on this form. You will be given a signed and dated copy of this consent form to keep for your records.
If the investigator will also be your child’s treating doctor, this will be discussed with you.

**Purpose of the Research:**
Your child’s physician is a member of TARGet Kids! (Toronto Area Research Group) which is a network of SickKids child health researchers and community doctors dedicated to improving the health of young children.

With the aim of “health research for every child,” this network will collect medical evidence on common health problems affecting urban Canadian children. We have a special focus on measuring the nutritional health of children from birth to 10 years of age. This is the first group in Canada to study children in community settings with a goal to promote wellness and prevent disease. We are inviting you and your child(ren) to participate in this exciting new initiative.

This study aims to collect information on nutrition in healthy children 0-10 years of age. Nutrition will be measured using the Nutrition Screening Tool for Every Preschooler (NutriSTEP™) which is a 17 item questionnaire that was developed by dieticians and parents. Parents can fill out the questionnaire for their children. We would like to see how the questionnaire relates to growth measures in children and how easy it is to use the NutriSTEP™ in the Canadian doctor’s office. We will ask you to complete a short questionnaire on your child’s personality/behaviour so that we can learn more about the relationship between personality and nutrition in children. We will also ask your child to have blood tests to measure his/her nutritional health, such as cholesterol, iron, and vitamin D. These blood tests will be obtained and processed by experts from the Mount Sinai Services team.

**The goal of TARGet Kids! project is to collect information of 2400 children from different sites across Toronto. We anticipate that 500 of those kids will be recruited from St Michael’s Hospital.**

**Description of the Research:**
If you agree for your child to participate in this study, the following tests/assessments will be performed:

- **Questionnaires:** (i) NutriSTEP the Nutrition Screening Tool for Every Preschooler and for Toddler, a 17 item parent report of nutrition for young children; (ii) Nutrition and Health Questionnaire - a demographics, dietary, and physical activity questionnaire that focuses on nutrition, physical activity, sedentary behaviours in your child; (iii) the Infant Behavior Questionnaire, Early Childhood Behavior Questionnaire, Children’s Behavioural Questionnaire (CBQ); (iv) Nipissing District Developmental Tool; (v) Infant Toddler Checklist; (vi) Parenting Stress Index will be administered by the research assistant. Questionnaires will take approximately 25 minutes to complete at each visit. These assessments are not a part of standard care and are being administered only for research purposes.

- **Physical Examination:** Your child’s height/length, weight, waist circumference and blood pressure will be recorded annually up to 10 years of age. Aside from waist circumference, these measures are part of the normal annual visit for children. We will also record your height, weight and waist circumference. All of these measurements will occur at each of your child’s regularly scheduled annual visits between 1 and 10 years of age.
- **Blood Collection:** A trained health professional experienced with pediatric blood collection will take a small blood sample from your child to measure laboratory tests related to nutrition such as vitamin levels, iron levels, and cholesterol. These measurements will occur annually during your child’s regularly scheduled visits between 1 and 10 years of age.

- **Collection of Health Information:** We will obtain your child’s previous measurements (height, weight, head circumference, blood pressure) using previous records from your physician. We may also collect additional health information on your child using an OHIP number. No additional visits to your doctor are required.

**Collection of Health information from Ontario’s Health Administration Databases**
As your child grows and develops, we would like to obtain information on their health using information routinely collected by the Ontario health care system. This information is housed in multiple health administration databases. In order to do this, we will use your child’s OHIP number to link data securely to such databases.

**Privacy and Confidentiality using Health Administration Data**
Health information held in Ontario’s health administration databases is used solely for research and statistical purposes. All data are kept confidential to protect the privacy of individuals through the use of multiple secure methods.
By signing this form, you are authorizing access to your medical records by the study personnel and the St. Michael’s Hospital Research Ethics Board. Such access will be used only for the purpose of verifying the authenticity and accuracy of the information collected for the study, without violating your confidentiality to the extent permitted by applicable laws and regulations.

The data collected for the study will be kept for 7 years after completion of the project and will be securely destroyed after that.

**Future Research:**
Although your child will only be followed for this study until 10 years of age at your family physician’s office, your child will be followed further into the future. We would like to see how characteristics, lifestyles, and nutritional habits of young children under 10 affect future health outcomes in adulthood such as stroke, heart disease and diabetes.

In the future, our research team may approach you to participate in other studies with the aim of improving children’s health, which may include prevention of diabetes, heart disease, Vitamin D deficiency and other health conditions. The research will be explained to you and your consent will be asked for at that time.

**Potential Harms, Discomforts or Inconvenience:**
We will collect a small blood sample (4-7 mL of blood) from your child’s arm using a needle. Topical anesthetic cream (EMLA or Ametop) will be offered to minimize discomfort from the blood draw. There may be slight discomfort, bruising or redness that will usually disappear in a few days. Blood collection is usually a quick process (about 5 minutes) and at other times it can
require a little more time. Participating in this project will lengthen your child’s doctor’s visit by up to 25 minutes.

**Potential Benefits:**
Your child may benefit from participating in the TARGet Kids study by having the NutriSTEP™ results available to you and to your child’s doctor who will discuss the results with you in more detail. The NutriSTEP™ questionnaire will provide you with guidance about your child's nutrition and how it may be improved. We will also give you some helpful handouts to take home with healthy living tips for your child. Society may benefit from the nutrition study if the questionnaire is found to be useful for doctors in their offices. This quick questionnaire may help guide doctors to make useful recommendations to improve their patients’ health.

Your child may benefit from participating in the TARGet Kids! study by having his or her blood measured as the results will be provided to your child’s doctor with your permission. This could inform your doctor if your child might need a nutritional supplement or changes in diet or lifestyle. In addition to knowing one has helped understand dietary and physical activity habits and related health measures such as growth and laboratory tests, your child may be helping other children in Canada and the world. Participants themselves (and/or family member or friend) could potentially be a patient at a paediatric health centre, and benefit directly from the results obtained from this study.

**Alternatives to Participation:**
Participation in this study is completely voluntary, and declining to participate will in no way affect your care at this or any other health care facility.

**Privacy and Confidentiality:**
All persons involved in the study, including the study investigators and coordinators (hereby referred to as “study staff”), the study sponsor (Canadian Institute of Health Research), are committed to respecting your privacy. They will make every effort to keep your personal health information private and confidential in accordance with all applicable privacy legislations, including the Personal Health Information Protection Act (PHIPA) of Ontario.

Personal health information is any information that could be used to identify you and includes your:
- name,
- address,
- date of birth,
- new or existing medical records, that includes types, dates and results of medical tests or procedures.

Any personal identifying information (such as your child’s name) will be “de-identified” by replacing personal identifying information with a “study number”. The study coordinator and principal investigator here at St. Michael's Hospital are in control of the study code key, which is needed to connect the study data to your child. The link between the study number and your
child’s personal identity will be safeguarded by the St. Michael’s Hospital principal investigator.

We will respect your privacy. No information about who your child is will be given to anyone outside of the study or be published without your permission, unless required by law. All information collected during this study, including your child’s personal health information, will be kept confidential and will not be shared with anyone outside the study unless required by law. For example, the law could make us give information about you if a child has been abused, if your child has an illness that could spread to others, if your child or someone else talks about harming themselves or others, or if the court orders us to give them the study papers.

SickKids Clinical Research Monitors, employees of the funders (PORT), or the regulator may see your questionnaire responses or your child’s blood test results to monitor on the study. By signing this consent form, you agree to let these people look at this information.

The data produced from this study will be stored in a secure, locked location at the Hospital for Sick Children. Only members of the research team (and maybe those described above) will have access to the data. This could include external research team members.

You or your child will not be named in any reports, publications, or presentations that may come from this study.

If you decide to withdraw from the study, the information that was collected before your child left the study will still be used. No new information will be collected without your permission, unless required for your child’s safety.

**Publication of Results**
The results of this research study will be presented at various conferences, and will be published in scientific journals. Your name will not appear in any presentation or publication.

**Costs to Participation and Reimbursement:**
Participants in this study will not be reimbursed. Participation in this study may result in added costs (e.g. parking expenses) for which you will not be reimbursed for.

**Compensation for Injury:**
If your child suffers an injury from participating in this study, medical care will be provided to your child in the same manner as you would ordinarily obtain any other medical treatment. In no way does signing this form waive your legal rights nor release the study doctor(s), or involved institutions from their legal and professional responsibilities.

**Participation and Withdrawal:**
Participation in this study is totally voluntary. If you prefer for your child to not take part, you do not have to give a reason. You and your child will continue to have access to customary care at St. Michael’s Hospital or any other hospital you choose to visit. If you choose to take part in the study, but later change your mind you can withdraw participation at any time, without
giving a reason and without any effect on the care that your child or your family may receive at St. Michael’s Hospital. If you decide to withdraw from the study, the information that was collected before your child left the study will still be used. No new information will be collected without your permission, unless required for your child’s safety.

**New Findings or Information:**
New information that we get while we are doing this study may affect your decision to take part in this study. If this happens, we will tell you about this new information. And we will ask you again if you still want to be in the study.

**Research Ethics Board Contact**
If you have any questions regarding your rights as a research participant, you may contact the Chair of the Research Ethics Board at your hospital.
- St. Michael's, 416-864-6060 ext 2557 during business hours.
- The Hospital for Sick Children, 416-813-5718

**Study Contact**
You may ask the study doctor and his/her staff any questions you may have about this study at any time.

If you have any questions or would like additional information please contact:
- **Marina Khovratovich** at 416-813-2129
- **Dr. Jonathon Maquire**, Principal Investigator at St. Michael’s Hospital at (416) 813-2129 (Mon-Fri: 9AM-5PM) or 416 864-5431 (Hospital Locating)
- **Or Dr. Patricia Parkin**, Overall Principal Investigator at the Hospital for Sick Children, at (416) 813-6933

**Statement of Consent:**
**Study Title: TARGet Kids!** Measuring nutrition in young preschool-aged children in the primary care practice setting

By signing this form, I acknowledge that:
1) The study has been explained to me and all my questions have been answered to my satisfaction.
2) I have been informed of the alternatives to my child participating in this study, including the right not to participate and the right to withdraw my child from the study without compromising the quality of medical care at St. Michael’s for me and for my other members of my family.
3) The potential risks, harms and discomforts have been explained to me and I also understand the benefits (if any) of participating in the research study.
4) I understand that I have not waived my legal rights (and the legal right’s of my child) nor released the investigators, sponsors, or involved institutions from their legal and professional duties.
5) I know that I may ask now, or in the future, any questions ask questions about the study.
6) I acknowledge that I may be asked to participate in future studies.
7) I have been assured that the records relating to me and my child’s care will be kept confidential and that no information will be released or printed that would disclose personal identity without my permission, unless require by law.
8) I have been given sufficient time to read and understand the above information.

_I agree, or consent, that my child ________________________ may take part in this study._
Name of Child Participant

**Future Use of Study Data and Identifying Information**
I consent that study data may used for future studies without contacting me if all identifying information is removed so that the data cannot be identified as my child’s (i.e. de-identified).

<table>
<thead>
<tr>
<th>Yes</th>
<th>No</th>
<th>Initial _________</th>
</tr>
</thead>
</table>

**Communication With Your Child’s Family Physician**
Your family physician will be contacted if there are any abnormal results. Would you like us to communicate normal results of your testing with your family physician?

<table>
<thead>
<tr>
<th>Yes</th>
<th>No</th>
<th>Initial _________</th>
</tr>
</thead>
</table>

Printed Name of Parent/Legal Guardian
Parent/Legal Guardian’s signature
Date

_I consent to providing my height, weight and waist circumference as required by the study._

Printed Name of Parent/Legal Guardian
Parent’s/ Legal Guardian’s Signature
Date

_I have explained the study to the above participant explained the nature and purpose, the potential benefits, and possible risks associated with participation in this research study. I have answered all questions._

Name & Position of Person
Signature of Person
Date

Obtaining Consent (Print)
Obtaining Consent
APPENDIX B – FOOD SOURCES OF VITAMIN D
## Food Sources of Vitamin D

<table>
<thead>
<tr>
<th>Food</th>
<th>Serving Size</th>
<th>Vitamin D (IU)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Vegetables and Fruit</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Vegetables</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Shiitake mushrooms, cooked</td>
<td>125 mL (½ cup)</td>
<td>77</td>
</tr>
<tr>
<td>Mushrooms, cooked</td>
<td>125 mL (½ cup)</td>
<td>63</td>
</tr>
<tr>
<td>Mushrooms, raw</td>
<td>125 mL (½ cup)</td>
<td>39</td>
</tr>
<tr>
<td><strong>Juice</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Orange juice, fortified with vitamin D</td>
<td>125 mL (½ cup)</td>
<td>53</td>
</tr>
<tr>
<td><strong>Grain Products</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>This food group contain very little of this nutrient.</td>
<td></td>
</tr>
<tr>
<td><strong>Milk and Alternatives</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Milk</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3.3% homo, 2%, 1%, skim, chocolate milk</td>
<td>250 mL (1 cup)</td>
<td>106-112</td>
</tr>
<tr>
<td>Skim milk powder</td>
<td>24 g (will make 250 mL of milk)</td>
<td>106</td>
</tr>
<tr>
<td><strong>Milk Alternatives (check the label to see if the product has been fortified)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Goat's milk, fortified with vitamin D</td>
<td>250 mL (1 cup)</td>
<td>103</td>
</tr>
<tr>
<td>Almond or oat beverage, fortified with vitamin D</td>
<td>250 mL (1 cup)</td>
<td>90</td>
</tr>
<tr>
<td>Rice or soy beverage, fortified with vitamin D</td>
<td>250 mL (1 cup)</td>
<td>88</td>
</tr>
<tr>
<td><strong>Yogurt (check the label to see if the product has been fortified)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yogurt (plain, fruit bottom), fortified with vitamin D</td>
<td>175 g (¼ cup)</td>
<td>7-60</td>
</tr>
<tr>
<td>Yogurt beverage, fortified with vitamin D</td>
<td>200 mL</td>
<td>43-50</td>
</tr>
<tr>
<td><strong>Meat and Alternatives</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Salmon</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Humpback/pink, raw or cooked</td>
<td>75 g (2 ½ oz)</td>
<td>646-765</td>
</tr>
<tr>
<td>Sockeye/red or chinook, canned or cooked</td>
<td>75 g (2 ½ oz)</td>
<td>585-678</td>
</tr>
<tr>
<td>Chum/keta, raw or cooked</td>
<td>75 g (2 ½ oz)</td>
<td>476-561</td>
</tr>
<tr>
<td>Sockeye/red or chinook, raw</td>
<td>75 g (2 ½ oz)</td>
<td>530</td>
</tr>
<tr>
<td>Coho, wild, raw or cooked</td>
<td>75 g (2 ½ oz)</td>
<td>456-507</td>
</tr>
<tr>
<td>Humpback/pink, canned</td>
<td>75 g (2 ½ oz)</td>
<td>436</td>
</tr>
<tr>
<td><strong>Tuna</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bluefin, raw or cooked</td>
<td>75 g (2 ½ oz)</td>
<td>540-690</td>
</tr>
<tr>
<td>Skipjack, raw or cooked</td>
<td>75 g (2 ½ oz)</td>
<td>300-381</td>
</tr>
<tr>
<td>White, canned with water</td>
<td>75 g (2 ½ oz)</td>
<td>60</td>
</tr>
<tr>
<td><strong>Other Fish and Seafood</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eel, raw or cooked</td>
<td>75 g (2 ½ oz)</td>
<td>699</td>
</tr>
<tr>
<td>Swordfish, cooked</td>
<td>75 g (2 ½ oz)</td>
<td>594</td>
</tr>
<tr>
<td>Herring, Atlantic, pickled</td>
<td>75 g (2 ½ oz)</td>
<td>510</td>
</tr>
<tr>
<td>Whitefish, lake, cooked</td>
<td>75 g (2 ½ oz)</td>
<td>450</td>
</tr>
<tr>
<td>Roe, raw</td>
<td>75 g (2 ½ oz)</td>
<td>363</td>
</tr>
<tr>
<td>Food Item</td>
<td>Serving Size</td>
<td>Calories</td>
</tr>
<tr>
<td>--------------------------------------------------------------------------</td>
<td>--------------</td>
<td>----------</td>
</tr>
<tr>
<td>Sardines, Pacific, canned</td>
<td>75 g (2 ½ oz)</td>
<td>360</td>
</tr>
<tr>
<td>Oysters, wild, raw or cooked</td>
<td>75 g (2 ½ oz)</td>
<td>240</td>
</tr>
<tr>
<td>Mackerel, canned</td>
<td>75 g (2 ½ oz)</td>
<td>189</td>
</tr>
<tr>
<td>Herring, Atlantic, cooked</td>
<td>75 g (2 ½ oz)</td>
<td>162</td>
</tr>
<tr>
<td><strong>Meat and Alternatives</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Veal, various cuts, cooked</td>
<td>75 g (2 ½ oz)</td>
<td>45-72</td>
</tr>
<tr>
<td>Liver, turkey, cooked</td>
<td>75 g (2 ½ oz)</td>
<td>54</td>
</tr>
<tr>
<td>Deli meat (pork, beef, salami, bologna)</td>
<td>75 g (2 ½ oz)/ 3 slices</td>
<td>42-54</td>
</tr>
<tr>
<td>Egg, yolk, cooked</td>
<td>2 large</td>
<td>42-52</td>
</tr>
<tr>
<td>Heart or kidney, beef, cooked</td>
<td>75 g (2 ½ oz)</td>
<td>51</td>
</tr>
<tr>
<td>Sausage, pork or beef (smoked link, Polish, Kielbas), cooked</td>
<td>75 g (2 ½ oz)</td>
<td>30-48</td>
</tr>
<tr>
<td>Pork, ribs, cooked</td>
<td>75 g (2 ½ oz)</td>
<td>24-39</td>
</tr>
<tr>
<td>Pate, goose liver, smoked</td>
<td>75 g (2 ½ oz)</td>
<td>36</td>
</tr>
<tr>
<td>Beef, brisket, cooked</td>
<td>75 g (2 ½ oz)</td>
<td>33</td>
</tr>
<tr>
<td>Ground meat (beef, turkey), cooked</td>
<td>75 g (2 ½ oz)</td>
<td>12-30</td>
</tr>
<tr>
<td><strong>Fats and Oils</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cod liver oil</td>
<td>5 mL (1 tsp)</td>
<td>427</td>
</tr>
<tr>
<td>Margarine</td>
<td>5 mL (1 tsp)</td>
<td>27</td>
</tr>
</tbody>
</table>


[http://www.ajcn.org/content/80/6/1710S.full.pdf+html]

Vitamin D fortification in the United States and Canada: current status and data needs
APPENDIX C – DIETARY REFERENCE INTAKES FOR CALCIUM AND VITAMIN D
levels in the range of 40 to 50 nmol/L (16 to 20 ng/mL) was desirable, an AI was established based on evidence that maintaining serum 25OHD included changes in bone density and fracture risk. For infants, average requirements for these life stage groups. The factors taken into more information about maximal population coverage than they do about standard deviations used for other groups. In fact, available data provide group than for the younger group. Therefore, the RDA value for persons average for 97.5 percent of the population should be greater for this older ability around these estimates in the case of bone health for older persons. This suggests that the assumption about the variance associated with cov distribution suggested no effect due to age. However, there is notable vari

### TABLE S-2 Vitamin D Dietary Reference Intakes by Life Stage (amount/day)

<table>
<thead>
<tr>
<th>Life Stage Group</th>
<th>AI</th>
<th>EAR</th>
<th>RDA</th>
<th>UL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infants</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 to 6 mo</td>
<td>400 IU (10 µg)</td>
<td>—</td>
<td>—</td>
<td>1,000 IU (25 µg)</td>
</tr>
<tr>
<td>6 to 12 mo</td>
<td>400 IU (10 µg)</td>
<td>—</td>
<td>—</td>
<td>1,500 IU (38 µg)</td>
</tr>
<tr>
<td>Children</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1–3 y</td>
<td>—</td>
<td>400 IU (10 µg)</td>
<td>600 IU (15 µg)</td>
<td>2,500 IU (63 µg)</td>
</tr>
<tr>
<td>4–8 y</td>
<td>—</td>
<td>400 IU (10 µg)</td>
<td>600 IU (15 µg)</td>
<td>3,000 IU (75 µg)</td>
</tr>
<tr>
<td>Males</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9–13 y</td>
<td>—</td>
<td>400 IU (10 µg)</td>
<td>600 IU (15 µg)</td>
<td>4,000 IU (100 µg)</td>
</tr>
<tr>
<td>14–18 y</td>
<td>—</td>
<td>400 IU (10 µg)</td>
<td>600 IU (15 µg)</td>
<td>4,000 IU (100 µg)</td>
</tr>
<tr>
<td>19–30 y</td>
<td>—</td>
<td>400 IU (10 µg)</td>
<td>600 IU (15 µg)</td>
<td>4,000 IU (100 µg)</td>
</tr>
<tr>
<td>31–50 y</td>
<td>—</td>
<td>400 IU (10 µg)</td>
<td>600 IU (15 µg)</td>
<td>4,000 IU (100 µg)</td>
</tr>
<tr>
<td>51–70 y</td>
<td>—</td>
<td>400 IU (10 µg)</td>
<td>600 IU (15 µg)</td>
<td>4,000 IU (100 µg)</td>
</tr>
<tr>
<td>&gt; 70 y</td>
<td>—</td>
<td>400 IU (10 µg)</td>
<td>800 IU (20 µg)</td>
<td>4,000 IU (100 µg)</td>
</tr>
<tr>
<td>Females</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9–13 y</td>
<td>—</td>
<td>400 IU (10 µg)</td>
<td>600 IU (15 µg)</td>
<td>4,000 IU (100 µg)</td>
</tr>
<tr>
<td>14–18 y</td>
<td>—</td>
<td>400 IU (10 µg)</td>
<td>600 IU (15 µg)</td>
<td>4,000 IU (100 µg)</td>
</tr>
<tr>
<td>19–30 y</td>
<td>—</td>
<td>400 IU (10 µg)</td>
<td>600 IU (15 µg)</td>
<td>4,000 IU (100 µg)</td>
</tr>
<tr>
<td>31–50 y</td>
<td>—</td>
<td>400 IU (10 µg)</td>
<td>600 IU (15 µg)</td>
<td>4,000 IU (100 µg)</td>
</tr>
<tr>
<td>51–70 y</td>
<td>—</td>
<td>400 IU (10 µg)</td>
<td>600 IU (15 µg)</td>
<td>4,000 IU (100 µg)</td>
</tr>
<tr>
<td>&gt; 70 y</td>
<td>—</td>
<td>400 IU (10 µg)</td>
<td>800 IU (20 µg)</td>
<td>4,000 IU (100 µg)</td>
</tr>
<tr>
<td>Pregnancy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>14–18 y</td>
<td>—</td>
<td>400 IU (10 µg)</td>
<td>600 IU (15 µg)</td>
<td>4,000 IU (100 µg)</td>
</tr>
<tr>
<td>19–30 y</td>
<td>—</td>
<td>400 IU (10 µg)</td>
<td>600 IU (15 µg)</td>
<td>4,000 IU (100 µg)</td>
</tr>
<tr>
<td>31–50 y</td>
<td>—</td>
<td>400 IU (10 µg)</td>
<td>600 IU (15 µg)</td>
<td>4,000 IU (100 µg)</td>
</tr>
<tr>
<td>Lactation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>14–18 y</td>
<td>—</td>
<td>400 IU (10 µg)</td>
<td>600 IU (15 µg)</td>
<td>4,000 IU (100 µg)</td>
</tr>
<tr>
<td>19–30 y</td>
<td>—</td>
<td>400 IU (10 µg)</td>
<td>600 IU (15 µg)</td>
<td>4,000 IU (100 µg)</td>
</tr>
<tr>
<td>31–50 y</td>
<td>—</td>
<td>400 IU (10 µg)</td>
<td>600 IU (15 µg)</td>
<td>4,000 IU (100 µg)</td>
</tr>
</tbody>
</table>

NOTE: AI = Adequate Intake; EAR = Estimated Average Requirement; IU = International Units; RDA = Recommended Dietary Allowance; UL = Tolerable Upper Intake Level.

### BOX S-3

**Potential Indicators of Adverse Outcomes for Excess Intake of Calcium and Vitamin D**

**Calcium**
- Hypercalcemia
- Hypercalciuria
- Vascular and soft tissue calcification
- Nephrolithiasis (kidney stones)
- Prostate cancer
- Interactions with iron and zinc
- Constipation

**Vitamin D**
- Intoxication and related hypercalcemia and hypercalciuria
- Serum calcium
- Measures in infants: retarded growth, hypercalcemia
- Emerging evidence for all-cause mortality, cancer, cardiovascular risk, falls and fractures
APPENDIX D – GEOGRAPHICAL ETHNICITY DIVISIONS^{22,135,156}
Geographical ethnicity divisions

North American Aboriginal (Inuit, Métis, First Nations, etc)
  o Inuit
  o Métis
  o First Nations
  o Cree
  o Mi’kmaq (Micmac)

Western European
  o Andorra
  o Austria
  o Belgium
  o Denmark
  o England
  o Finland
  o France
  o Germany
  o Greece
  o Iceland
  o Italy
  o Ireland
  o Liechtenstein
  o Luxembourg
  o Malta
  o Monaco
  o Norway
  o Netherlands
  o Portugal
  o Scotland
  o Spain
  o Sweden
  o Switzerland
  o Wales
  o Vatican City

Eastern European
  o Albania
  o Armenia
  o Azerbaijan
  o Belarus
  o Bosnia and Herzegovina
  o Bulgaria
  o Croatia
  o Cyprus
  o Czech Republic
  o Estonia
- Georgia
- Hungary
- Kosovo
- Latvia
- Lithuania
- Macedonia
- Moldova
- Montenegro
- Poland
- Romania
- Russia
- San Marino
- Serbia
- Slovakia
- Slovenia
- Ukraine

**East Asian (Chinese)**

**East Asian (Korean)**

**East Asian (Japanese)**

**South Asian (East Indian, Pakistani, Sri Lankan, etc)**
- Afghanistan
- Bangladesh
- Bhutan
- India
- Maldives
- Nepal
- Pakistan
- Sri Lanka

**Southeast Asian (e.g. Vietnamese, Cambodian, Malaysian, Filipino, etc)**
- Cambodia
- Indonesia
- Laos
- Malaysia
- Philippines
- Singapore
- Thailand
- Vietnam

**West Asian (e.g. Iranian, Afghan, Palestinian, etc)**
- Armenia
- Azerbaijan
- Bahrain
- Cyprus
- Georgia
- Iraq
- Israel
- Jordan
- Kuwait
- Lebanon
- Oman
- Palestinian Territories
- Qatar
- Saudi Arabia
- Syria
- Turkey
- United Arab Emirates
- Yemen

**Latin American (e.g. Argentinean, Chilean, Costa Rican, Mexican, etc)**
- Cuba
- Dominican Republic
- Costa Rica
- El Salvador
- Guatemala
- Honduras
- Mexico
- Nicaragua
- Panama
- Argentina
- Bolivia
- Brazil
- Chile
- Colombia
- Ecuador
- Falkland Island (Malvina)
- Paraguay
- Peru
- Uruguay
- Venezuela

**East African (e.g. Ethiopian, Kenyan, Malagasy (Madagascar), Somali, etc)**
- Burundi
- Comoros
- Djibouti
- Eritrea
- Ethiopia
- Kenya
- Madagascar
- Malawi
- Mauritius
- Mayotte
- Mozambique
- Reunion
- Rwanda
- Seychelles
- Somalia
- Tanzania
- Uganda
- Zambia
- Zimbabwe

**Middle African (e.g. Cameroonian, Chadian, Congolese, etc)**
- Angola
- Cameroon
- Central African Republic
- Chad
- Congo (Brazzaville)
- Congo, Democratic Republic of the
- Equatorial Guinea
- Gabon
- Sao Tome and Principe

**Northern African (e.g. Moroccan, Algerian, Egyptian, Sudanese, etc)**
- Algeria
- Egypt
- Libyan Arab Jamahiriya
- Morocco
- Sudan
- Tunisia
- Western Sahara

**Southern African (e.g. Botswana, South African, etc)**
- Botswana
- Lesotho
- Namibia
- South Africa
- Swaziland

**Western African (e.g. Ghanaian, Nigerian, Guinean, etc)**
- Benin
- Burkina Faso
- Cape Verde
- Cote d’Ivoire (Ivory Coast)
o Gambia
o Ghana
o Guinea
o Guinea-Bissau
o Liberia
o Mali
o Mauritania
o Niger
o Nigeria
o Saint Helena
o Senegal
o Sierra Leone
o Togo

Caribbean Region (e.g. Jamaican, Trinidadian/Tobagonian, etc)
 o Anguilla
 o Antigua and Barbuda
 o Aruba
 o Bahamas
 o Barbados
 o British Virgin Islands
 o Cayman Islands
 o Dominica
 o Grenada
 o Guadeloupe
 o Haiti
 o Jamaica
 o Belize
 o Guyana
 o French Guyana
 o Suriname
 o Martinique
 o Montserrat

Indian-Caribbean (e.g. Guyana with origins in India)
 o Indians in Barbados
 o Indo-Grenadians
 o Indians in Guadeloupe
 o Indo-Martiniquais
 o Indo-Jamaican
 o Indo-Trinidadian and Tobagonian
 o Indians in Belize
 o Indians in French Guiana
 o Indo-Guyanese
 o Indo-Surinamese
 o Indo-Caribbean American
- British Indo-Caribbean community
- Indians in Venezuela

Oceania (e.g. Samoan, Fijian, etc)
- Fiji
- French Polynesia
- Guam
- Kiribati
- Marshall Islands
- Micronesia
- New Caledonia
- Papua New Guinea
- Samoa
- Samoa, American
- Solomon, Islands
- Tonga
- Vanuatu

Australia or New Zealand
APPENDIX E – DATA CREATION PLAN (DCP)
**DCP - Evaluation of the reclassification of ethnicity: a TARGet Kids! study**

<table>
<thead>
<tr>
<th>Name and Number of Study</th>
<th>Evaluation of the reclassification of ethnicity: a TARGet Kids! study</th>
</tr>
</thead>
</table>
| **PIs** Student          | Jonathon Maguire  
                          Jessica Omand                                              |
| **DCP update history**   | Version 1 - Aug 30th, 2012                                   |
| **Short Description of Research Question** | To evaluate the degree of agreement between the reclassified ethnicity variable and parent completed closed-ended ethnicity variable |
| **List of Datasets Used** | TARGet Kids! Baseline and follow-up  
                          • NHQ (Ethnicity question)                                  |
| **Time of Data extraction** | June 2012                                                   |

**Defining the Cohort**

<table>
<thead>
<tr>
<th><strong>Cohort</strong></th>
<th>Children aged 1 to 5 who attend well-child visits at a primary care pediatrician’s or family physician’s office who have participated in TARGet Kids! at least 2 times.</th>
</tr>
</thead>
</table>
| **Exclusion Criteria for TARGet Kids!** | • Children with associated health conditions affecting growth (e.g. failure to thrive, cystic fibrosis  
                                     • Children with a chronic condition(s) except for asthma  
                                     • Children with severe developmental delay  
                                     • Families who are not fluent in English  
                                     • Parents who did not answer the ethnicity question  
                                     • Parents who did not complete a TARGet Kids! follow-up appointment |
| **Size of Cohort** | Number of children recruited from October 2008 to June 2012 who completed baseline and follow-up questionnaires on different dates. |

**Time Frame Definitions**

<table>
<thead>
<tr>
<th><strong>Accrual Start/End Dates</strong></th>
<th>October 2008 to June 2012</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Max Follow-up Date</strong></td>
<td>June 2012</td>
</tr>
</tbody>
</table>

**Variable Definitions**

<table>
<thead>
<tr>
<th><strong>Exposure definition</strong></th>
<th>Reclassified ethnicity variable (parent reporting open-ended ethnicity, race and country of birth responses converted into an ethnicity variable)</th>
</tr>
</thead>
</table>
| **Baseline Characteristics** | Population descriptors:  
                         • Age  
                         • Sex  
                         • Median household income  
                         • Reclassified ethnicity  
                         • 19 category ethnicity |
| **Predictor Definition** | Reclassified ethnicity variable |
| **Outcome Definition**   | 19 category ethnicity question |
Outline of Analysis Plan – Objective 1

<table>
<thead>
<tr>
<th>Outcome variables</th>
<th>• Percentage of ethnicity classifications in perfect agreement</th>
</tr>
</thead>
</table>
| Analysis Plan     | • Frequency statistics will be run on both pre and post ethnicity variables to populate Table 1, baseline descriptors  
|                   | • Percentage of ethnicity classifications in agreement will be described  
|                   | • Simple Kappa statistic will be calculated |
| Tables and Figures| Table 1: Population descriptors (see above)  
|                   | Figure 1: Frequency distributions of the reclassified ethnicity variable and 19 category new ethnicity question  
|                   | Table 2: Kappa coefficients for the agreement and association of the two ethnicity categorizations  
|                   | Table 3: Cross-Tabulation of reclassified ethnicity and 19 category parent identified ethnicity (See other document)  
|                   | Table 4: Percentage of cases in perfect agreement (sensitivity) between reclassified ethnicity and parent completed ethnicity responses, using parent reported as the reference  
|                   | Table 5: Trends in reclassification error |

List of variables for analysis

<table>
<thead>
<tr>
<th>Variable</th>
<th>Variable Name in dataset</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subject ID</td>
<td>Subject</td>
</tr>
<tr>
<td>Date of initial visit</td>
<td>VISITDT</td>
</tr>
<tr>
<td>Date of visit</td>
<td>VISITDT</td>
</tr>
<tr>
<td>Visit type (screening, follow-up)</td>
<td>TBD</td>
</tr>
<tr>
<td>Maternal ethnicity (reclassified)</td>
<td>Ethnicity_maternal</td>
</tr>
<tr>
<td>Paternal ethnicity (reclassified)</td>
<td>Ethnicity_paternal</td>
</tr>
</tbody>
</table>
| 19 category ethnicity (discrete categories) | 1. Eastern European (Polish, Russian, Croatian, etc)  
| - Maternal and Paternal       | 2. Western European (English, French, Portuguese, etc)  
|                               | 3. East Asian (Chinese)  
|                               | 4. East Asian (Korean)   
|                               | 5. East Asian (Japanese) |
|                               | 6. South Asian (East Indian, Pakistani, Sri Lankan, etc)  
|                               | 7. Southeast Asian (e.g. Vietnamese, Malaysian, Filipino, etc)  
|                               | 8. West Asian (e.g. Iranian, Afghan, Palestinian, etc)  
|                               | 9. East African (e.g. Ethiopian, Kenyan, Somali, etc)  
|                               | 10. Middle African (e.g. Cameroonian, Chadian, Congolese, etc)  
|                               | 11. Northern African (e.g. Moroccan, Algerian, Egyptian, Sudanese, etc)  
|                               | 12. Southern African (e.g. Botswana, South African, etc)  
|                               | 13. Western African (e.g. Ghanaian, Nigerian, Guinean, etc)  
|                               | 14. Latin American (e.g. Argentinean, Costa Rican, Mexican, etc)  
|                               | 15. Caribbean Region (e.g. Jamaican, Trinidadian/Tobagonian, etc)  
|                               | 16. Indian-Caribbean (e.g. Guyana with origins in India)  
|                               | 17. North American Aboriginal (Inuit, Métis, First Nations, etc)  
|                               | 18. Oceania (e.g. Samoan, Fijian, etc)  
|                               | 19. Australian or New Zealander  
|                               | 20. Other (please specify)  |
### Population Description – participants taking vitamin D supplements versus not taking vitamin D supplements

<table>
<thead>
<tr>
<th>Child characteristics</th>
<th>Participants taking vitamin D supplements (N=850)</th>
<th>Participants not taking vitamin D supplements (N=690)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Frequency (%)</td>
<td>Median (Range)</td>
</tr>
<tr>
<td>Age, months</td>
<td></td>
<td>37 (12-76)</td>
</tr>
<tr>
<td>Sex, male</td>
<td>422 (50)</td>
<td>363 (53)</td>
</tr>
<tr>
<td>Skin pigmentation</td>
<td>739 (87)</td>
<td>581 (84)</td>
</tr>
<tr>
<td>Weight, zBMI</td>
<td>0.14 (-3.1-3.8)</td>
<td>0.2 (-3.0-3.9)</td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mixed western</td>
<td>580 (68)</td>
<td>424 (61)</td>
</tr>
<tr>
<td>Mixed western/non-western</td>
<td>176 (21)</td>
<td>169 (24)</td>
</tr>
<tr>
<td>East Asian &amp; Southeast Asian</td>
<td>49 (6)</td>
<td>41 (6)</td>
</tr>
<tr>
<td>Southwest Asian</td>
<td>31 (4)</td>
<td>39 (6)</td>
</tr>
<tr>
<td>African &amp; Caribbean</td>
<td>14 (2)</td>
<td>17 (2)</td>
</tr>
<tr>
<td>Season</td>
<td></td>
<td></td>
</tr>
<tr>
<td>May-Sept (summer)</td>
<td>376 (44)</td>
<td>335 (49)</td>
</tr>
<tr>
<td>Current cow’s milk intake, mL</td>
<td>500 (0-1250)</td>
<td>500 (0-1250)</td>
</tr>
<tr>
<td>Outdoor Play</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-4 hours/week</td>
<td>359 (42)</td>
<td>270 (39)</td>
</tr>
<tr>
<td>5-7 hours/week</td>
<td>491 (58)</td>
<td>420 (61)</td>
</tr>
<tr>
<td>Median household income</td>
<td>56,000 (0-335,000)</td>
<td>56,000 (0-210,000)</td>
</tr>
<tr>
<td>Non-western immigrant</td>
<td>217 (26)</td>
<td>204 (30)</td>
</tr>
<tr>
<td>25-hydroxyvitamin D</td>
<td>87 (11-242)</td>
<td>80 (12-267)</td>
</tr>
</tbody>
</table>
### Population Description – Western immigrants versus Canadian born families

<table>
<thead>
<tr>
<th>Child characteristics</th>
<th>Family immigrated from a Western country (N=288)</th>
<th>Family born in Canada (N=831)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Frequency (%)</td>
<td>Median (Range)</td>
</tr>
<tr>
<td>Age, months</td>
<td>37 (12-70)</td>
<td>35 (12-75)</td>
</tr>
<tr>
<td>Sex, male</td>
<td>155 (54)</td>
<td>409 (49)</td>
</tr>
<tr>
<td>Skin pigmentation</td>
<td>277 (96)</td>
<td>784 (94)</td>
</tr>
<tr>
<td>Type I, II or III</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight, zBMI</td>
<td>0.2 (-3.0-3.8)</td>
<td>0.2 (-3.0-3.0)</td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mixed western</td>
<td>256 (89)</td>
<td>702 (84)</td>
</tr>
<tr>
<td>Mixed western/non-western</td>
<td>31 (11)</td>
<td>112 (13)</td>
</tr>
<tr>
<td>East Asian &amp; Southeast Asian</td>
<td>0 (0)</td>
<td>8 (1)</td>
</tr>
<tr>
<td>Southwest Asian</td>
<td>1 (0.4)</td>
<td>8 (1)</td>
</tr>
<tr>
<td>African &amp; Caribbean</td>
<td>0 (0)</td>
<td>1 (0.1)</td>
</tr>
<tr>
<td>Season</td>
<td></td>
<td></td>
</tr>
<tr>
<td>May-Sept (summer)</td>
<td>119 (41)</td>
<td>396 (48)</td>
</tr>
<tr>
<td>Current cow’s milk intake, mL</td>
<td>500 (0-1250)</td>
<td>500 (0-1250)</td>
</tr>
<tr>
<td>Vitamin D supplementation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>146 (51)</td>
<td>487 (59)</td>
</tr>
<tr>
<td>Outdoor Play</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-4 hours/week</td>
<td>121 (42)</td>
<td>278 (33)</td>
</tr>
<tr>
<td>5-7 hours/week</td>
<td>167 (58)</td>
<td>553 (67)</td>
</tr>
<tr>
<td>Median household income</td>
<td>56,000 (0-154,000)</td>
<td>58,000 (0-335,000)</td>
</tr>
<tr>
<td>Vitamin D</td>
<td>91 (12-267)</td>
<td>83 (19-246)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Child characteristics</th>
<th>Non-Western immigrant children (N=18)</th>
<th>Children born in Canada with non-Western immigrant parent (N=403)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Frequency (%)</td>
<td>Median (Range)</td>
</tr>
<tr>
<td>Age, months</td>
<td>48 (12-68)</td>
<td></td>
</tr>
<tr>
<td>Sex, male</td>
<td>7 (39)</td>
<td>214 (53)</td>
</tr>
<tr>
<td>Skin pigmentation</td>
<td>8 (44)</td>
<td>251 (62)</td>
</tr>
<tr>
<td>Type I, II or III</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight, zBMI</td>
<td>-0.3 (-1.8-1.6)</td>
<td>-0.13 (-3.1-3.9)</td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mixed western</td>
<td>2 (11)</td>
<td>44 (11)</td>
</tr>
<tr>
<td>Mixed western/non-western</td>
<td>5 (28)</td>
<td>197 (49)</td>
</tr>
<tr>
<td>East Asian &amp; Southeast Asian</td>
<td>7 (39)</td>
<td>75 (19)</td>
</tr>
<tr>
<td>Southwest Asian</td>
<td>3 (17)</td>
<td>58 (14)</td>
</tr>
<tr>
<td>African &amp; Caribbean</td>
<td>1 (6)</td>
<td>29 (7)</td>
</tr>
<tr>
<td>Season</td>
<td></td>
<td></td>
</tr>
<tr>
<td>May-Sept (summer)</td>
<td>11 (61)</td>
<td>185 (46)</td>
</tr>
<tr>
<td>Current cow’s milk intake, mL</td>
<td>500 (0-1250)</td>
<td>500 (0-1250)</td>
</tr>
<tr>
<td>Vitamin D supplementation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>10 (56)</td>
<td>207 (51)</td>
</tr>
<tr>
<td>Outdoor Play</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-4 hours/week</td>
<td>7 (39)</td>
<td>223 (55)</td>
</tr>
<tr>
<td>5-7 hours/week</td>
<td>11 (61)</td>
<td>180 (45)</td>
</tr>
<tr>
<td>Median household income</td>
<td>62,000 (15,000-99,000)</td>
<td>50,000 (0-269,000)</td>
</tr>
<tr>
<td>Vitamin D</td>
<td>78 (61-189)</td>
<td>80 (11-210)</td>
</tr>
</tbody>
</table>
Population Description: <50 nmol/L Western versus non-Western and >50 nmol/L Western versus non-Western

<table>
<thead>
<tr>
<th>Child characteristics</th>
<th>&lt;50 nmol/L (N=81)</th>
<th>&gt;50 nmol/L (N=1459)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Western born (N=31)</td>
<td>Non-western Immigrants (N=50)</td>
</tr>
<tr>
<td></td>
<td>Frequency (%)</td>
<td>Median (Range)</td>
</tr>
<tr>
<td>Age, months</td>
<td>38 (12-65)</td>
<td>37 (12-70)</td>
</tr>
<tr>
<td>Sex, male</td>
<td>12 (39)</td>
<td>27 (54)</td>
</tr>
<tr>
<td>Skin pigmentation</td>
<td>Type I, II or III</td>
<td>15 (48)</td>
</tr>
<tr>
<td>Weight, zBMI</td>
<td>0.2 (-2.4-1.9)</td>
<td>0.2 (-2.6-2.7)</td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mixed western</td>
<td>2 (6)</td>
<td>41 (82)</td>
</tr>
<tr>
<td>Mixed western/non-western</td>
<td>11 (35)</td>
<td>9 (18)</td>
</tr>
<tr>
<td>East Asian &amp; Southeast Asian</td>
<td>6 (19)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Southwest Asian</td>
<td>8 (26)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>African &amp; Caribbean</td>
<td>4 (13)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Season</td>
<td>May-Sept (summer)</td>
<td>10 (32)</td>
</tr>
<tr>
<td>Current cow’s milk intake, mL</td>
<td>500 (0-1250)</td>
<td>500 (0-1250)</td>
</tr>
<tr>
<td>Vitamin D supplementation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>11 (35)</td>
<td>24 (48)</td>
</tr>
<tr>
<td>Outdoor Play</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-4 hours/week</td>
<td>19 (61)</td>
<td>20 (40)</td>
</tr>
<tr>
<td>5-7 hours/week</td>
<td>12 (39)</td>
<td>30 (60)</td>
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<tr>
<td>Median household income</td>
<td>37,000 (16,000-81,000)</td>
<td>56,000 (26,000-335,000)</td>
</tr>
<tr>
<td>Vitamin D</td>
<td>41 (11-49)</td>
<td>42 (12-49)</td>
</tr>
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</table>