THE ROLE OF THE CARNITINE PALMITOYLTRANSFERASE 1A (CPT1A) p.P479L VARIANT IN INUIT INFANT AND CHILD HEALTH OUTCOMES

by

SORCHA COLLINS

BSc, The University of Victoria, 2005

M.Sc., The University of British Columbia, 2010

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The following individuals certify that they have read, and recommend to the Faculty of Graduate and Postdoctoral Studies for acceptance, the dissertation entitled:

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Examining Committee:

Dr. Laura Arbour, Department of Medical Genetics
Supervisor

Dr. Suzanne Lewis, Department of Medical Genetics
Supervisory Committee Member

Dr. Angela Devlin, Department of Pediatrics
University Examiner

Dr. Pascal Lavoie, Department of Pediatrics
University Examiner

Additional Supervisory Committee Members:

Dr. Angela Brooks-Wilson, Department of Medical Genetics
Supervisory Committee Member

Dr. Patricia Janssen, School of Population and Public Health
Supervisory Committee Member

ABSTRACT

Nunavut leads the country for a number of adverse early child health outcomes, including infant hospitalizations for lower respiratory tract infection (LRTI; ~306/1,000), otitis media (85%) and infant mortality (21.5/1,000). The p.P479L (c.1436C>T, rs80356779) variant of carnitine palmitoyltransferase 1A (CPT1A), an enzyme required for long-chain fatty acid oxidation in the liver, pancreas, lymphocytes and other tissues, is prevalent in northern Indigenous populations of Canada. Although evidence is limited, the p.P479L variant has been associated with childhood infectious illness, hypoglycemia, seizures and with unexpected infant death and infant death due to infection. This dissertation investigated the association of p.P479L variant with infant and child morbidity (up to five years) in the context of relevant prenatal, postnatal and socioeconomic variables in a cohort of 2523 Inuit children living in Nunavut born from Jan-2010 to Dec-2013. The results demonstrate that the CPT1A p.P479L variant was associated with infectious illness in early childhood including LRTI admission, otitis media and gastroenteritis, after adjustment for socioeconomic and other confounding variables. In considering the potential effect on fatty acid oxidation and possible risk for hypoglycemia, I also determined that the incidence of neonatal hypoglycemia was higher in term Inuit newborns than expected, and, although not statistically significant, p.P479L homozygous and heterozygous newborns had higher incidence of neonatal hypoglycemia than non-carriers. Taken together, these results suggest that children homozygous for the p.P479L variant may be more susceptible to infectious illness compared to non-carriers and may be more likely to experience hypoglycemia in the first days of life. My results replicate and expand on previous, smaller studies. Multidisciplinary local input and community engagement is indicated to determine if routine neonatal glucose screening and/or other management is indicated for Inuit infants. Further studies are needed to understand

the role of the p.P479L variant in infection susceptibility, immune and inflammatory response and vaccination effectiveness in Inuit communities.

LAY SUMMARY

Infants and children in Nunavut have high rates of infectious illness and hypoglycemia (low blood sugar) in the first days of life. More than 80% of Inuit children in Nunavut have the p.P479L variant of the gene encoding carnitine palmitoyltransferase 1A (*CPT1A),* which is important in the way fat is used for energy. Infants with the p.P479L variant were twice as likely to be admitted to hospital for lung infection, have middle ear infections, need major dental interventions and had a trend towards increased risk of hypoglycemia in the first days of life compared to those without the variant. The p.P479L variant is common in Inuit, Alaska Native and some British Columbia First Nations populations. The results of this study may help to inform programs to prevent for infection in young children. Further studies to understand whether the variant reduces immunity to infections are warranted.

PREFACE

The concept of this research arose from a CIHR Partnership in Health Services Improvement (PHSI) grant (FRN 122187), led by Dr. Laura Arbour and in partnership with the Government of Nunavut Department of Health (GNDoH), Nunavut Tunngavik Inc. (NTI) and the Qaujigiartiit Health Research Centre (QHRC). NTI is responsible for ensuring the implementation of and adherence to the Nunavut Land Claims Agreement and advocates for policies and programs that enhance Inuit well-being, which includes healthy children. The QHRC is a community-led research institute that fosters local leadership and engagement in research activities involving the health and well-being of Nunavummiut. This research was conducted with ethics approval and regulatory approval from University of British Columbia (H13-02699), University of Victoria (14-210) and University of Manitoba (HS17732 (H2014:225)) Research Ethics Boards and the Nunavut Research Institute.

I was responsible for all major areas of the project, including project planning, data acquisition, data cleaning, coding, linkage, analysis and interpretation, and writing and revising all chapters of this dissertation. I developed the data analysis plan in consultation with Dr. Laura Arbour and in conjunction with Dr. Anders Erickson, who provided statistical expertise. Data acquisition included planning and managing the collection of medical chart and genotype data, building the comprehensive chart review database and training and mentoring chart reviewers from a distance who visited 18 remote Nunavut communities. I coordinated retrieval, cataloguing and shipping of stored dried blood spots for testing. I developed, submitted and maintained ethics applications, data sharing agreements and supplementary funding proposals. *CPT1A* genotyping for the study was conducted by the newborn screening programme at Cadham Provincial Laboratory in

Winnipeg Manitoba for all Kivalliq region newborns and Newborn Screening Ontario at the Children's Hospital of Eastern Ontario for all Kitikmeot and Qikiqtaaluk region newborns. Portions of this dissertation have been published or will be submitted for publication.

A version of Chapter 2 will be submitted for publication: **SA Collins**, S Edmunds, G Healey Akearok, GE Hildes-Ripstein, A Miners, C Rockman-Greenberg, L Arbour. The health status of Inuit infants and children residing in Nunavut (2010-2014).

- I developed the study design and research questions with Dr. Arbour, Dr. Rockman-Greenberg, Ms. Edmunds (NTI), Dr. Healey Akearok (QHRC), Dr. Hildes-Ripstein and Dr. Miners. I managed and coordinated all data collection, conducted data merging, cleaning, coding and analysis, wrote and revised the manuscript and prepared all figures.
- The research was conducted with ethics approval and regulatory approval from University of British Columbia (H13-02699), University of Victoria (14-210) and the Nunavut Research Institute.

A version of Chapter 3 has been published in Paediatrics & Child Health: **SA Collins**, GE Hildes-Ripstein, S Edmunds, JR Thompson, A Miners, C Rockman-Greenberg, L Arbour. Neonatal hypoglycemia and the CPT1A p.P479L variant in term newborns: a retrospective cohort study of Inuit newborns from Kivalliq Nunavut. Paediatrics and Child Health, Apr 2020, pxa339.

- I developed the study design and research questions with Dr. Arbour, Dr. Rockman-Greenberg, Dr. Hildes-Ripstein, Dr. Miners and Ms. Edmunds (NTI). Dr. Rockman-Greenberg and Dr. Hildes-Ripstein coordinated and conducted the chart review and Dr.

Rockman-Greenberg and Robert Thompson coordinated *CPT1A* genotyping and Robert Thompson managed the genotyping at the Cadham Provincial Laboratory in Winnipeg Manitoba. I developed the data analysis plan with Dr. Arbour, Dr. Rockman-Greenberg and Dr. Erickson. I conducted all data cleaning, coding, linkage and analysis, interpreted results, wrote and revised the manuscript and prepared all figures. All authors critically edited and approved the final manuscript as submitted.

- The research was conducted with ethics approval and regulatory approval from University of British Columbia (H13-02699), University of Victoria (14-210) and University of Manitoba (HS17732, H2014:225) Research Ethics Boards and was developed and conducted in partnership with the NTI.

A version of Chapter 4 will be submitted for publication: **SA Collins**, S Edmunds, G Healey Akearok, JR Thompson, A Erickson, GE Hildes-Ripstein, A Miners, M Somerville, DM Goldfarb, C Rockman-Greenberg, L Arbour. Association of the carnitine palmitoyltransferase 1A (CPT1A) p.P479L arctic gene variant with infectious illness in early childhood.

- I developed the study design and research questions with Dr. Arbour, Dr. Rockman-Greenberg, Ms. Edmunds, Dr. Healey Akearok, Dr. Goldfarb, Dr. Hildes-Ripstein and Dr. Miners. I developed the data analysis plan with Dr. Arbour, Dr. Rockman-Greenberg and Dr. Erickson. Dr. Rockman-Greenberg and Mr. Robert Thompson coordinated *CPT1A* genotyping as in Chapter 3. Dr. Somerville coordinated access to stored dried blood spot samples in Alberta and *CPT1A* genotyping was conducted at the newborn screening program at the Children's Hospital of Eastern Ontario. I managed and coordinated all data collection, conducted data cleaning, coding, linkage and statistical

analysis, interpreted the results and wrote and revised the manuscript and prepared all figures. All authors critically edited and approved the final manuscript as submitted.

- The research was conducted with ethics approval and regulatory approval from University of British Columbia (H13-02699), University of Victoria (14-210) and University of Manitoba (HS17732, H2014:225) Research Ethics Boards and the Nunavut Research Institute. The study was developed and conducted in partnership with the GNDoH, NTI and the QHRC.

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LIST OF ABBREVIATIONS

BC: British Columbia

CHD: Congenital heart defect

CPS: Canadian Paediatric Society

CPT1A: carnitine palmitoyltransferase 1A

CWB: community well-being index

FAO: fatty acid oxidation

FAOD: fatty acid oxidation disorder

GE: gastroenteritis

HWE: Hardy-Weinberg equilibrium

IDM: infant of a diabetic mother

IM: infant mortality

LGA: large for gestational age

LRTI: lower respiratory tract infection

MS: multiple sclerosis

NBS: newborn screening

NH: neonatal hypoglycemia

OM: otitis media

PTB: preterm birth

RSV: respiratory syncytial virus

SES: socioeconomic status

SGA: small for gestational age

SIDS: sudden infant death syndrome

SUDI: sudden unexpected death in infancy

Term-NRF: term newborn (≥37weeks gestation) with no risk factors for neonatal hypoglycemia

TB: tuberculosis

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Throughout my program, I have been privileged to have the encouragement and support of many family members and friends for which I am deeply grateful, especially my mother, Mary, my very good friend Katrina Madsen, and, of course, my supportive and ever patient young son, Ronan, and husky, Brenna.

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DEDICATION

For my guiding lights, Ronan and Brenna.

CHAPTER 1. INTRODUCTION

1.1 PURPOSE OF STUDY

This study focusses on determining the impact of the p.P479L genetic variant of carnitine palmitoyltransferase 1A (*CPT1A*) on infant and child health outcomes in Nunavut; specifically, neonatal hypoglycemia and infectious illness, after adjusting for other relevant birth, postnatal and socioeconomic variables.

1.2 STUDY RATIONALE

Nunavut is Canada's largest jurisdictional landmass, with 25 remote communities along the arctic coastline accessible only by air or sea, and 39,000 inhabitants, of which 85% self-identify as Inuit [1,2]. Nunavut leads the country for a number of adverse early child health outcomes [3–5], including infant hospital admissions for lower respiratory tract infection (LRTI; 234-306/1,000), amongst the highest worldwide [4,6–8] and an infant mortality rate four times the national average (21.5 vs 4.5/1,000 live births) [9], as well as high rates of otitis media and anemia in early childhood [10,11].

One genetic factor, the p.P479L variant (c.1436C>T; rs80356779) of the enzyme carnitine palmitoyltransferase 1A (CPT1A) has been identified as a possible contributor to the higher rates of LRTI and infant mortality in Nunavut [12–18]. CPT1A is a fatty acid oxidation (FAO) enzyme in the liver and other tissues, encoded by the *CPT1A* gene, and is required to use long chain fats for energy during periods of fasting or prolonged exercise [19]. Classic CPT1A deficiency is a rare autosomal recessive disorder, presenting in infancy as hypoketotic

hypoglycaemia and metabolic decompensation, which can progress to seizures, brain damage and sudden death. The p.P479L gene variant of *CPT1A* is common in the Northern Indigenous populations of Canada, Alaska and Greenland [17,20–22]. The p.P479L variant has been associated with a number of adverse early child health outcomes, including hypoglycaemia [13,14], seizures [23], hospital admission for infection in early childhood [15,18], sudden unexpected infant death and infant death due to infection [12,16,17], suggesting that those with the variant may have greater susceptibility to infection. However, studies to date have not been able to include other important postnatal and socioeconomic variables that are also associated with these outcomes. This dissertation addresses the link between the p.P479L genetic variant and infant and child morbidity within the broader context of social determinants of infant and child health outcomes in Nunavut.

1.2.1 Research objectives

1. Report on the recent status of the health of Inuit infants and children in Nunavut and compare outcomes between regions and to previous studies for Inuit inhabited regions of Canada.
2. Determine the incidence of neonatal hypoglycemia in Inuit children residing in Kivalliq Nunavut and whether the p.P479L variant is associated with increased risk of neonatal hypoglycemia.
3. Determine regional prevalence of the p.P479L variant in Inuit children in Nunavut and determine the associated risk for infectious illness in early childhood associated with the p.P479L variant in the broader context of critical perinatal, postnatal and socioeconomic covariates.

1.3 BACKGROUND AND LITERATURE REVIEW

1.3.1 Infant and child health in Nunavut

Inuit children in Canada experience high rates of adverse birth and early childhood health outcomes compared to non-Indigenous Canadian children [3–5]. The majority of Canadian Inuit reside in Nunavut, which has a the highest rate of preterm birth (<37weeks gestation) in Canada (14% vs 7.8%), admissions in infancy for lung infection (234-306/1,000 infants), otitis media (85% of Inuit preschool children) and infant mortality (21.5/1,000, Table 1.1) [4,6,9,10,24]. The leading causes of infant mortality in Nunavut are sudden infant death syndrome (SIDS), sudden unexpected death in infancy (SUDI) and death due to infection (1999-2011) [12].

Table 1.1 Perinatal characteristics and outcomes for Nunavut and Canadian infants

Characteristic	Period	Nunavut	Canada
Population [1]	2018	38,139	37,057,765
Inuit population [25]	2011	85%	0.20%
Births/year (mean) [26]	2010-13	856	379,254
Birth/1,000 people [26]	2010-13	25/1,000	11/1,000
Maternal age <20yrs [27]	2010-13	21%	3%
Preterm births (<37wks) [24]	2013	14%	7.8%
Congenital anomalies [28]	2000-09	59.3/1,000LB	40.8/1,000LB
Infant mortality [9]	2010-13	21.5/1,000LB	4.5/1,000LB
(SIDS/SUDI) [12]	1999-2011	6.1/1,000LB	0.5/1,000LB
Breastfeeding initiation [29]	2010-13	76%	89%
Breastfeeding >6 months [29]	2010-13	29%	27%
Maternal prenatal smoking* [30,31]	NU: 2000-05	81%	10.5%
>10 cigarettes/day [30,31]	CDA: 2005-06	30%	7%
Food insecurity** [32,33]	2007-08	56%	11%
Household crowding [34]	2006	43%	7%

*Data for prenatal smoking in Canada taken from the Maternity Experiences Survey, 2005-06
**Data for food insecurity in Canada for households with children less than five years of age, 2011. SIDS: sudden infant death syndrome, SUDI: sudden unexpected death in infancy

The Inuit people of Canada primarily live in one of four Canadian Northern regions which are collectively called the Inuit Nunangat ("Inuit Homeland"; Figure 1.1), Nunavik in Northern Quebec, Nunatsiavut in Northern Labrador, the Inuvialuit region of the Northwest Territories, and in Nunavut [35]. Nunavut is Canada's largest jurisdictional land mass, covering the most northern and eastern area of Canada. The territory has 39,000 inhabitants and is home to the largest Inuit population in Canada [1,2]. An average of 850 infants are born to Nunavut residents (Nunavummiut) each year; 90% of those to Inuit women [2,36]. The 25 communities of Nunavut are small and spread along the coastline in the three regions: Qikiqtaaluk, Kivalliq and Kitikmeot. Most Nunavut communities are isolated geographically and are accessible only by air and sea.

The Nunavut health care system relies on nurse-run health centres in each community. The Qikiqtani General Hospital is the only hospital in Nunavut and is located in the territorial capital, Iqaluit, Qikiqtaaluk, which is the largest community with 7000 residents [25].Tertiary medical care for Nunavummiut requires air travel out of territory to Ontario (Qikiqtaaluk), Manitoba (Kivalliq, Kitikmeot), the Northwest Territories (Kitikmeot) and Alberta (Kitikmeot) [37,38]. Within Nunavut, births occur at the Qikiqtani General Hospital in Iqaluit or at low-risk midwife birthing centres in Cambridge Bay and Rankin Inlet. Approximately half of births to Nunavummiut occur out of territory in Yellowknife, Alberta, Winnipeg and Ottawa [26].

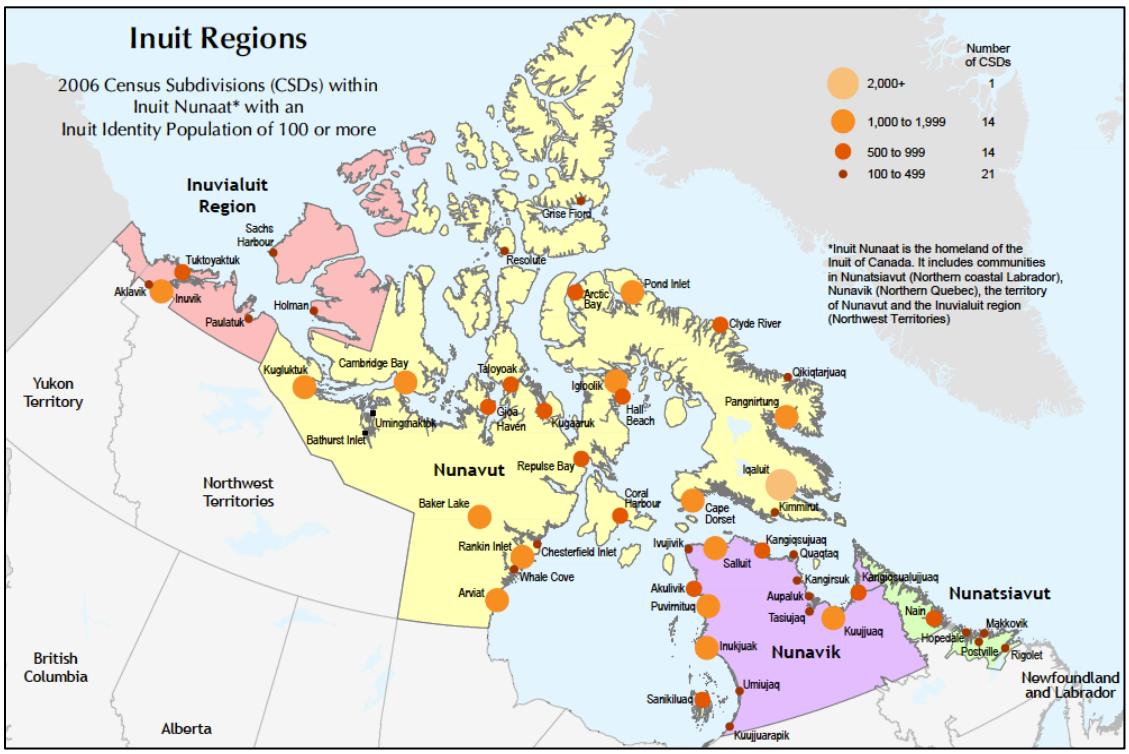

Figure 1.1 Inuit Regions of Canada from the 2006 Census Subdivisions (CSDs) within Inuit Nunangat with an Inuit identity population of 100 or more
Source: 2006 Census of Canada. [39] Produced by the Geography Division, Statistics Canada, 2007©

1.3.2 Lower respiratory tract infections in infants and children in Nunavut

Inuit infants in Nunavut have the highest reported rates of hospitalization for LRTI in Canada, with rates between 234 to 306 admissions/1,000 infants [4,6–8]. Numerous studies have identified respiratory syncytial virus (RSV) as a key contributor to LRTI and infant hospitalisation in Nunavut [8,6,40], which has been identified as a major concern in the Canadian Paediatric Society 2011 RSV guidelines [41]. The peak RSV seasons in Nunavut are from January to June and there are between 93 to 168 cases reported each year (2008-12) [42]. Vaccination for RSV is a possible method for reducing the high rate of infant hospitalizations for

LRTI in Nunavut; however, RSV vaccination requires monthly intramuscular injections for a maximum of five doses.

A number of risk factors for severe LRTI [43–45] are common in Nunavut (Table 1.1), including preterm births [24] and tobacco smoke exposure [46]. Household crowding and food insecurity are also prevalent in Nunavut, Statistics Canada reports that Inuit children are six times more likely to live in crowded homes than non-Indigenous Canadian children (43% versus 7%) [47]. The Nunavut Inuit Child Health Survey, a cross-sectional study held between 2007 and 2008 of 374 Inuit children aged 3-5years (born between 2002-2005), found that 56% of Inuit children were food insecure (moderate or severe) and that 70% of Nunavut households with children aged 3-5years were either moderately or severely food insecure [32] compared to 11% of Canadian households with children under the age of five in 2007/08 [33]. Data from the Canadian Community Health Survey shows that food insecurity in Nunavut communities has been increasing in the past ten years. In 2007/08, 31.9% of all households in Nunavut reported moderate or severe food insecurity, which increased to 36.7% in 2011/12 [33], 46.1% in 2015/16 and 49.4% in 2017/18 [48]. In 2011, the national northern food subsidy program transitioned to a market-driven food retail subsidy program called Nutrition North Canada. An analysis of the new system reported that food insecurity in Nunavut has increased by 13.2% since the implementation of the new program [49].

In a case-control study of Inuit children born between January 2002 to March 2003 living in Qikiqtaaluk Nunavut, Banerji et al.[6] found that hospital admission for LRTI in the first two years of life was associated with prenatal smoking (OR:4.0, 95%CI:1.1-14.6), not breastfeeding

(<2weeks; OR:3.6, 95%CI:1.2-11.5) and household crowding (>5 people living in the home; OR:2.5, 95%CI:1.1-6.1). Of note, half of the infants in the study had respiratory syncytial virus (RSV) [6]. Congenital heart defects are also associated with increased risk for infant admission for LRTI [40,45] and Nunavut has a rate of septal heart defects that is 3-4 times that of other Canadian jurisdictions [50]. A study of Inuit births to Qikiqtaaluk residents between 2000 and 2005 determined that infants with heart defects had a much higher rate of hospital admission for LRTI (826/1,000) and were more than twice as likely to be admitted to hospital for LRTI than infants without congenital anomalies [40].

Although severe LRTI in infancy has been found to be associated with wheezing and asthma in later life in the general population [51,52], the long-term impacts of the high rates of LRTI in Nunavut have not been well investigated. However, one cross-sectional survey of preschool aged Inuit children in all three regions of Nunavut reported that chronic cough and wheezing was common, and wheezing was significantly associated with severe LRTI in the previous 12 months. The authors also reported that tobacco smoke in the home was also associated with severe LRTI in the first two years of life [53].

1.3.3 Other infectious illness in Nunavut

Inuit infants in Nunavut also have high rates of other infectious diseases, including otitis media (middle ear infections), tuberculosis and *Haemophilus influenzae*. Otitis media is highly prevalent in Inuit children in Nunavut, 85% of preschoolers received treatment at least once for an ear infection, which is 1.7 times the national average (50% of children) [10,54]. Otitis media is divided into two main types, acute otitis media and otitis media with effusion. Acute otitis

media is an infection of the middle ear with acute onset of signs and symptoms caused by middle ear inflammation accompanied by fluid. Otitis media with effusion is the presence of fluid in the middle ear without signs of infection. Fluid in the middle ear causes pressure that prevents the tympanic membrane from vibrating properly, decreasing sound conduction and hearing [55]. Otitis media and draining ears are associated with impaired hearing at five years of age and can have dramatic impacts on speech and language development and educational attainment [55–59].

Inuit people in Canada also have the highest reported rates of tuberculosis (TB) in Canada [60]. TB is caused by the *Mycobacterium tuberculosis* bacterium. When inhaled, the TB bacterium usually becomes dormant, resulting in a latent TB infection [61]. Risk of active TB is higher in those with immune deficiencies and in infants and young children due to their immature immune systems. Measures implemented in the 1970's to control TB, including health care providers visiting communities offering mass screening and treatment, were successful in reducing TB in Nunavut; however, rates began to climb when those measures were discontinued, and the rate of TB in Inuit regions of Canada is now 290 times that of non-Indigenous Canadians [60].

Northern Canada also has the highest rate of invasive *Haemophilus influenzae* type A in children under the age of two in the circumpolar region (1999–2006) [62]. Between 2000-2012, there were 89 cases of *Haemophilus influenzae* (a or b) infections in Nunavut; 50 cases were under the age of five, and 27 occurred during infancy [63]. *H. influenzae* was also a major contributor to infant death due to infection for Nunavut infants born between 1999 and 2011 [12].

1.3.4 Infant mortality in Nunavut

Nunavut has the highest infant mortality rates in Canada, which has remained consistently high since 1999 (21.5/1,000 live births, 2014-18). The rate of infant mortality in Nunavut is almost 2.5 times that of the Northwest Territories (6.5/1,000 live births), which borders Nunavut and has a similar birth rate (~660/year), and is 3.6 times the national average (4.9/1,000 live births) [9,24]. My review of infant mortality in Nunavut between 1999 and 2011 determined that the leading causes of infant mortality were sudden infant death syndrome (SIDS), sudden unexpected death in infancy (SUDI) and infectious illness (Table 1.2) [12].

Table 1.2 Age and cause specific mortality rates for infant deaths in Nunavut by region (1999-2011) and Canada (1998-2007)

	Qikiqtaaluk rate (95%CI)	**Kivalliq rate (95%CI)**	**Kitikmeot rate (95%CI)**	**Nunavut rate (95%CI)**	**Canada† rate (95%CI)**	**NU vs CDA OR (95%CI)**
Live births	4,859	2,817	1,539	9,215	1,065,647	
Infant death	10.9 (8.2-14.2)	13.1 (9.3-18.1)	16.9 (11.1-24.7)	12.7 (10.5-15.2)	5.2 (5.0-5.3)	2.5 (2.0-3.0)
Post-neonatal death	8.2 (5.9-11.2)	10.7 (7.2-15.2)	11.7 (7.0-18.4)	9.7 (7.8-11.9)	1.3 (1.3-1.5)	7.0 (5.6-8.6)
Cause of Death						
SIDS/SUDI	5.8 (3.8-8.32)	5.7 (3.3-9.2)	7.8 (4.0-13.6)	6.1 (4.6-7.9)	0.5 (0.5-0.6)	12.0 (8.9-15.8)
Infection	2.1 (1.0-3.8)	3.2 (1.5-6.1)	3.3 (1.1-7.6)	2.7 (1.8-4.0)	0.3 (0.3-0.3)	8.8 (5.6-13.2)
Respiratory	0.8 (0.2-2.1)	0.7 (0.1-2.6)	2.0 (0.4-5.7)	1.6 (0.9-2.7)	-	-
H. influenza	0.4 (0.1-1.5)	0.4 (0.01-2.0)	1.3 (0.2-4.7)	0.7 (0.2-1.4)	-	-

Crude mortality rates for Nunavut were calculated per 1,000 live births. †Canadian rates (excluding Ontario) of crude infant and post-neonatal mortality were calculated with available 1998-2007 data and of cause-specific mortality were calculated with 2003-2007 data, as reported by the Public Health Agency of Canada in the Perinatal Health Indicators for Canada 2011 report [64]. 95%CI: 95% confidence interval, CDA: Canada, NU: Nunavut. SIDS: sudden infant death syndrome, SUDI: sudden unexpected death in infancy. Adapted from Collins et al.[12]

Sudden Infant Death Syndrome (SIDS) is defined as the sudden death of an infant less than one year of age that cannot be explained after a thorough investigation is conducted, including a complete autopsy, examination of the death scene, and review of the clinical history [65]. SUDI, sometimes abbreviated as SUID (Sudden, Unexpected Infant Death), is a broader category defined as the sudden and unexpected death of an infant, which may be accompanied by an illness not normally expected to cause death, or may have risk factors present for overlay or asphyxia [66]. Due to diagnostic overlap, SIDS and SUDI are combined in this study to allow for comparison of rates across jurisdictions and periods [66].

The combined rate for SIDS and SUDI (6.1/1,000LB) was significantly higher than the national average of 0.5/1,000LB (OR:11.95, 95%CI:8.92-15.79). Infant death due to infection was the second leading cause of post-neonatal death in the study and respiratory infections led the infectious category, which has broader implications given the high rate of infant hospital admissions for LRTI. There are a number of risk factors associated with SIDS and SUDI, including environmental, developmental and genetic factors [67–70]; however, reducing exposure to maternal tobacco smoking and placing infants to sleep on their backs (supine) appears to over-ride inherent risk factors, reducing risk of asphyxia. Results from surveys of Nunavut mothers found that only 38-46% of mothers place their infants to sleep on their backs, compared to 77% for the rest of Canada [31,71]. In my 1999-2011 review, 70% of SIDS/SUDI cases had two or more sleep-related risk factors present including non-supine sleep position and/or bed-sharing with non-caregiver(s) [12]. Gene variants that cause metabolic disorders are also implicated in SIDS and SUDI; infants with inborn errors of metabolism are also at increased

risk of SIDS/SUDI, and undiagnosed fatty acid oxidation disorders account for an estimated 3-6% of SIDS/SUDI cases [70,72,73].

1.3.5 Summary of infant and child health in Nunavut

In Canada, Inuit populations of Canada experience rates of infectious illness that are even greater than those for First Nations and Metis children [4,8], likely due in large part to greater challenges accessing medical care in very remote communities along with housing inadequacies, food insecurity and a high prevalence of smoking and environmental tobacco smoke exposure [6,32,43–46,74,75]. Nunavut also has a high rate of congenital heart defects [50,76], which are also associated with increased risk of infant admission for LRTI [40,45]. Fatty acid oxidation disorders can also increase severity of infectious illness due to the inability to compensate for hypoglycemia [77]. In Nunavut, the p.P479L variant of the fatty acid oxidation enzyme, carnitine palmitoyltransferase 1A, has been identified as a possible contributor to adverse health outcomes of infants and children in Nunavut, including the higher rates of infectious illness and infant mortality.

1.3.6 Carnitine palmitoyltransferase 1A (CPT1A)

1.3.6.1 Carnitine palmitoyltransferase pathway

Carnitine palmitoyltransferase 1A (CPT1A) is a fatty acid oxidation enzyme expressed in the liver and other tissues and is required to use long-chain fatty acids (LCFAs) for energy during fasting or prolonged exercise [19,78]. CPT1A is located in the outer mitochondrial membrane and is a key regulatory point for flux of LCFAs through to fatty acid oxidation (FAO, also called beta oxidation) (Figure 1.2) in the liver and other tissues [79]. During periods of fasting, illness

and prolonged exercise, FAO in the liver provides ketone bodies (β-hydroxybutyrate and acetoacetate), which are used for energy by other tissues in lieu of glucose, especially the brain, since it is unable to metabolize LCFAs for energy during periods of low blood glucose.

The CPT pathway is normally only active during the fasted state (low blood glucose) and inactive during the fed state. Excess cellular glucose is converted into acetyl-CoA and then into malonyl-CoA by acetyl-CoA carboxylase (ACC). In the fed state, accumulation of malonyl-CoA inhibits CPT1A by allosteric binding of the CPT1A regulatory domain. In this way, malonyl-CoA is a critical signalling molecule for maintaining the energetic flux between fatty acid synthesis and FAO [78].

In the absence of dietary glucose ('fasted state'), stored glucose (glycogen) is depleted, and FAO is activated. During low blood glucose, pancreatic alpha cells secrete glucagon, which signals the liver to breakdown glycogen (glycogenolysis) and activate glucose production (gluconeogenesis) and fatty acid oxidation and subsequent ketogenesis through AMP-activated protein kinase (AMPK) mediated deactivation of ACC via phosphorylation [80–82]. Inactivation of ACC causes malonyl-CoA levels to drop, releasing CPT1A from inhibition [78]. Glucagon also signals *CPT1A* transcription through the transcription factor cAMP responsive element binding (CREB) protein [83]. Interestingly, glucagon secretion in pancreatic alpha cells is itself reliant on CPT1A activity. Glucagon secretion relies on ATP-dependant Na+/K+ pump; Briant et al.[84] found that blockade of CPT1A impaired glucagon secretion though loss of FAO production of ATP.

Released LCFAs from adipose tissue enter cells passively or by FA transporters like CD36 [85]. Once inside the cell, LCFAs are converted into LCFA-CoAs by acyl-CoA synthease (ACS) [86]. CPT1A then catalyses the first step of LCFA transport into the mitochondria by transferring the fatty acyl group from LCFA-CoA to carnitine. Carnitine translocase (CACT) transports the resulting LCFA-carnitine across the mitochondrial matrix to carnitine palmitoyltransferase 2 (CPT2), which replaces the carnitine with CoA (reversing the CPT1A reaction). Free carnitine returns to the cellular cytoplasm and LCFA-CoA is transported into the mitochondria for fatty acid oxidation (FAO) [78,79,87].

CPT1A is encoded by the gene *CPT1A*, located on chromosome 11 (11q13.1) [88]. There are two other CPT1 isoforms, CPT1B, the primary form expressed in the heart and skeletal muscle and encoded by the gene *CPT1B* on chromosome 22 (22q13.31) [88,89] and CPT1C, located in neurons and encoded by the gene *CPT1C* on chromosome 19 (19q13.3) [90,91]. CPT1A is the major hepatic isoform and is the primary form in a number of other tissues including fibroblasts, lymphocytes, pancreas, brain, spleen, lung, kidney, adipose tissue and hypothalamus [79,92]. CPT1A and B are localised in the mitochondrial outer membrane with active sites exposed to the cytosolic side of the membrane [93]. All three forms bind malonyl-CoA. Although CPT1B is the major form expressed in the adult heart, CPT1A is also present in fetal and neonatal heart tissue [94]. Unlike CPT1A and CPT1B, CPT1C is localized in the endoplasmic reticulum in neuron cells instead of the mitochondrial membrane. Although CPT1C binds LCFA-CoAs and malonyl-CoA, it has minimal catalytic activity and likely functions more in lipid metabolism sensing [91,95].

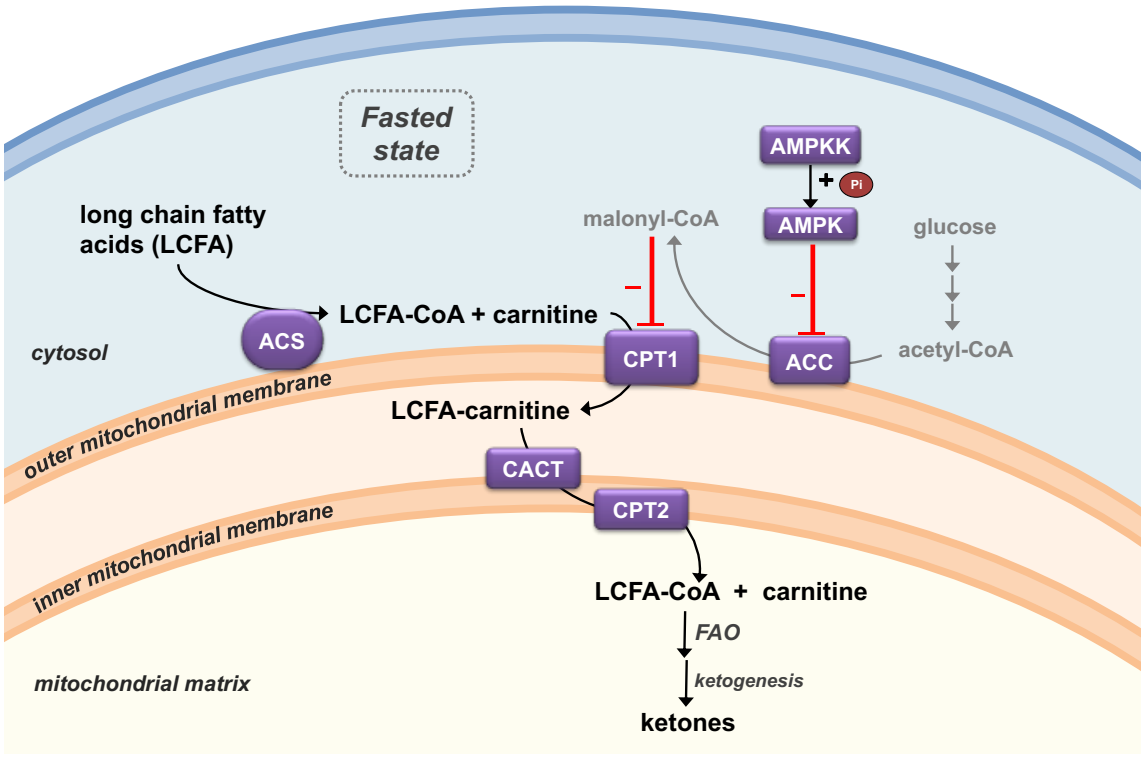

Figure 1.2 The carnitine palmitoyltransferase (CPT) pathway.
Long chain fatty acyls (LCFAs) require transport into the mitochondrion via the CPT pathway for oxidation. When glucose is present (the fed state), excess cellular glucose is converted into acetyl-CoA and then into malonyl-CoA by acetyl-CoA carboxylase (ACC). The increased concentration of Malonyl-CoA inhibits CPT1 activity. However, during low blood glucose (the fasted state), AMP-activated protein kinase kinase (AMPKK) activates AMP-activated protein kinase (AMPK), which deactivates ACC (via phosphorylation). CPT1 is released from inhibition as malonyl-CoA levels drop. CPT1 transfers the long chain acyl group from LCFA-CoA to carnitine. The resulting LCFA-carnitine is shuttled across to the inner mitochondrial membrane and converted back into LCFA-CoA by CPT2. LCFA-CoA is oxidized to produce energy via the FAO. In the liver, FAO product acetyl-CoA is converted into ketones for use by other tissues during fasting [78–80,86,87]. ACC, acetyl-CoA carboxylase: ACS, acyl-CoA synthetase: AMPK, AMP-activated protein kinase: AMPKK, AMP-activated protein kinase kinase: CPT1, carnitine palmitoyltransferase 1: CPT2, carnitine palmitoyltransferase 2: CACT, carnitine translocase.

CPT1A has two transmembrane domains (TM1 and TM2) and studies have found that CPT1A exists as a trimer or hexamer in the mitochondrial outer membrane (MOM) through binding of the transmembrane domain [96,97]. More recently, Lee et al. [98] reported that CPT1A forms hetero-oligomeric complexes with two other MOM proteins, long chain acyl-CoA synthetase and the MOM voltage-dependent anion channel (also known as the mitochondrial porin) that are responsible for channeling activated fatty acids through the MOM into the mitochondrial intermembrane space, although the functional relevance of these complexes still needs to be determined [98].

1.3.6.2 Expression of *CPT1A*

CPT1A gene expression and enzyme activity are regulated by the hormones insulin, glucagon and the thyroid hormone. Insulin is released from pancreatic beta cells in response to high blood glucose (hyperglycemia). By binding insulin growth factor receptor, insulin signals cells to decrease *CPT1A* expression and increases CPT1A sensitivity to malonyl-CoA [99,100]. In contrast, thyroid hormone signals the increased expression of *CPT1A* and reduces CPT1A sensitivity to malonyl-CoA [94]. Glucagon also increases *CPT1A* transcription and signals deactivation of ACC, releasing CPT1A from inhibition from malonyl-CoA [101,102]. CPT1A sensitivity to malonyl-CoA is also affected by the lipid content and the fluidity of the outer mitochondrial membrane [103,104]. Dietary omega-3 fatty acids also increase hepatic *CPT1A* expression [105,106]. Maternal diet and breastfeeding may also influence *CPT1A* expression and activity in infants. Neonate rats breastfed by dams eating a high fat diet had higher hepatic *Cpt1a* expression than neonates breastfed by dams consuming a high-carbohydrate diet [107].

1.3.7 Classic CPT1A deficiency

Classic CPT1A deficiency is a rare (1:500,000 to 1:1,000,000) autosomal recessive disorder presenting during infancy as hypoketotic hypoglycaemia and metabolic decompensation triggered by prolonged fasting and/or vomiting, often precipitated by active infection [108]. Mutations that cause classic CPT1A deficiency affect enzyme activity directly through functional mutations or indirectly by structural changes, reducing CPT1A activity to 0-15% of control [77,109,110]. Features of classic CPT1A deficiency may be accompanied by hepatic encephalopathy, heart dysfunction (cardiomegaly, fatty infiltration of the heart, bradycardia), liver enlargement and fatty infiltration [77,79,108,111]. These symptoms are exacerbated by fever, infection and dehydration. If left untreated, acute metabolic decompensation can progress to seizures and life-threatening events, and in rare cases, unexpected death [111].

Infants have limited glycogen stores and are highly dependent on long chain FAO during fasting [112]. Since glucagon secretion is dependent on CPT1A activity [84], stimulation of glycogen breakdown and gluconeogenesis may also be inadequate in CPT1A deficient patients. The combined effects of limited glycogen stores, impaired gluconeogenesis, FAO and subsequent ketogenesis in the liver, CPT1A deficient individuals are more susceptible during their first two years of life [77,84]. Classic CPT1A deficiency is one of many inborn errors of metabolism that can be detected during newborn screening using tandem mass spectrometry to measure the ratio of free carnitine to long chain acylcarnitine (C0/(C16+C18)>100) [113]. Treatment of classic CPT1A deficiency involves frequent feeding in the first years of life to avoid the need for utilization of fats for energy and the administration of oils rich in medium chain triglycerides [108].

1.3.8 The CPT1A p.P479L variant

The CPT1A p.P479L variant (c.1436C>T; rs80356779) was first described in 2001 by Brown et al.[109] in an adult British Columbia (BC) First Nations patient presenting with symptoms of recurrent muscle cramping, vomiting and loss of conscious. Skin fibroblasts studies found CPT2 activity was normal but CPT1A activity was diminished. Although the presentation was not consistent with CPT1A deficiency, the lower CPT1A activity (22% of control) suggested a possible mild variation of CPT1A deficiency. Sequencing of the *CPT1A* gene found the c.1436C>T missense mutation causing the substitution of leucine for proline at amino acid 479 (p.P479L). The proline found at 479 is highly conserved and the site is located close to the malonyl-CoA binding site, the regulator of CPT1A activity [114,115]. Remarkably, Brown et al.[109] also reported that the p.P479L variant enzyme had lower affinity for malonyl-CoA than wildtype and was active in both the fasted and fed states, maintaining a residual activity in the fed state that was four times control (0.094 vs 0.023 nmol/min/mg) [109], likely due to the proximity the to the malonyl-CoA binding site [114,115].

In 2009, Greenberg et al.[14] described investigations of CPT1A deficiency in seven patients: three Inuit children from a family in Nunavut, two Inuit children from a family in Northwest Territories and two First Nations children from a family British Columbia. All seven children had reduced CPT1A enzyme activity (2-16% of control) and were homozygous for the *CPT1A* p.P479L variant. The authors also reported a moderate reduction of FAO at normal body temperatures (37°C) in fibroblast studies. Fibroblast studies of one family study showed a further reduction of FAO at high temperatures (41°C) [14].

1.3.8.1 The p.P479L variant prevalence in Northern Indigenous populations

Since it was first described in 2001, numerous studies have determined that the p.P479L variant is prevalent in Northern coastal Indigenous populations of Alaska, Canada and Greenland (Table 1.3) [20–22]. In this way, the variant clusters in populations exposed to extreme arctic climates that historically subsisted on a marine based diet. To date, the variant has been reported to be absent in non-Indigenous populations, with the exception of two heterozygous individuals reported in the Exome Aggregation Consortium Data [22].

Table 1.3 Published allele frequencies for the *CPT1A* p.P479L variant.

Author	Region	Population	Age	n	p.P479L allele freq	p.P479L Hmz n (f)	p.P479L Het n	p.P479L NC n
Skotte et al 2017 [22]	Greenland	Greenlanders	≥16yrs	1570	0.74	nr	nr	nr
Rajakumar et al. 2012 [116]	Greenland	Inuit	~49yrs	1111	0.65	600 (0.54)	422	89
Zhou et al. 2015 [117]	Nunavik	Inuit	adults	113	0.96	nr	nr	nr
Collins et al. 2010 [20]	Nunavut	unk (90% Inuit)	1-30d	695	0.77*	442 (0.64)	186	67
	Qikiqtaaluk	unk	"	302	0.68*	162 (0.54)	89	51
"	Kivalliq	unk (95% Inuit)	"	243	0.83	170 (0.70)	62	11
"	Kitikmeot	unk (95% Inuit)	"	150	0.85	110 (0.73)	35	5
"	NWT	Inuvialuit	"	70	0.44	15 (0.21)	32	23
"	NWT	First Nations	"	233	0.04*	3 (0.01)	14	216
"	Yukon	unk	"	325	0.02	0	13	312
Sinclair et al. 2012 [17]	BC High Cluster	First Nations	≤2yrs	664	0.34	125 (0.19)	195	344
Lemas et al. 2012 [118]	Alaska	Yupik Eskimo	adults	1075	0.83	759 (0.71)	272	44
Gessner et al. 2011 [21]	Alaska	AN West/North	1-30d	255	0.70	132 (0.52)	95	28
Clemente et al. 2014 [119]	Northeast Siberia	Chukcki, Eskimo, Koryak	adults	25	0.68	10 (0.40)	nr	nr

p.P479L: homozygous for the p.P479L variant, p.P479L Het: heterozygous for the p.P479L variant, P.P479L NC: non-carrier of the p.P479L variant (wildtype), nr: not reported, unk: unknown. *CPT1A p.P479L variant not in Hardy-Weinberg Equilibrium.

The northern arctic Indigenous populations of Alaska, Canada and Greenland are divided into three linguistic branches; the Yupik, Aleut and Inuit/Inupiaq, all belonging to the Eskimo-Aleut family [35,120]. The Inuit/Inupiaq inhabit Northern Alaska, Canada and Greenland, the Yupik inhabit central and southern Alaska and the Chukotka peninsula of Russia, and the Aleut inhabit the Aleutian Islands of Alaska and the Commander Island of Russia. The Inuit people of Canada are descended from the Thule, who arrived in the Canadian arctic 1000 to 1600 AD [121,122].

In Canada, the p.P479L variant is prevalent in Nunavut, the Inuit of Nunavik, the Inuvialuit of Northwest Territories, and northern and coastal First Nations of British Columbia [20,17,117]. There was very low frequency of the variant in the inland First Nations populations of the NWT and Yukon and interior populations of BC. Most of the First Nations populations in Yukon and NWT are in-land populations, so this may be supportive of the hypothesis that the variant was historically beneficial to coastal populations.

The highest reported allele frequencies of the variant are in the Inuit of Nunavik (0.96), the Nunavut regions Kitikmeot (0.85) and Kivalliq (0.83) and the Yupik Eskimo of Alaska (0.83) [20,117,118]. The variant deviated from Hardy Weinberg Equilibrium (HWE) in infants born in 2006 residing in the Qikiqtaaluk region of Nunavut (allele frequency 0.77) [20], which was likely due to the inclusion of all births in the region since Inuit ancestry was not available for the study. However, the deviation from HWE may also have represented admixture in the population. Although there is no data for admixture in the Inuit people of Nunavut, European admixture is reported to be present in 8 to 13% of Inuit in Nunavik in northern Quebec [117,123]. In their 2015 study of fatty acid metabolism in the Inuit of Nunavik Quebec, Zhou et

al. [117] reported European admixture in 8% (9/113) of participants from 13 villages and a p.P479L variant allele frequency of 0.955 in the remaining 100 participants [117]. In a more recent study published in 2019, 13% of 170 Nunavik Inuit had evidence of European admixture [123].

Moltke et al.[124] report that European admixture is much higher in Greenlanders, with more than 80% of Greenlanders having some European admixture (approximately 25% of genome); however, the authors also report that Greenlanders residing in isolated and remote communities had very little or no European admixture. In a study measuring the association of fatty acid metabolism with the CPT1A p.P479L variant in 1570 Greenlanders, Skotte and colleagues also reported a high proportion of European admixture; however, study enrolment did not exclude non-Inuit participants and instead focussed on recruiting individuals born in Greenland with parents also born in Greenland [22]. As such, their results do not directly measure European admixture of the Inuit of Greenland. Interestingly, Skotte and colleagues also reported that when participants were stratified into levels of European admixture, the effect of the p.P479L variant was seen across all levels of admixture.

1.3.8.2 Historical advantage of the p.P479L variant

The presence of the p.P479L variant in the distantly related populations of Inuit and Inuvialuit of Nunavut and NWT, the Inuit of Greenland, the Yupik Alaskan Natives and the Chukcki, Eskimo, Koryak of Siberia indicates that this variant may have a place in the history of these populations (Figure 1.3). There is now evidence that the p.P479L variant predates the arrival of the Thule (the ancestors of the Inuit) in North America and there is also strong evidence of positive

selection for the variant. In their study of positive selection in arctic Indigenous populations, Clemente and colleagues [119] identified the p.P479L variant as one of the strongest reported signals of selective sweep in humans, likely occurring 6,000-23,000 years ago. These results have since been duplicated by studies of the Inuit in Nunavik [117,123] and Greenlanders [22].

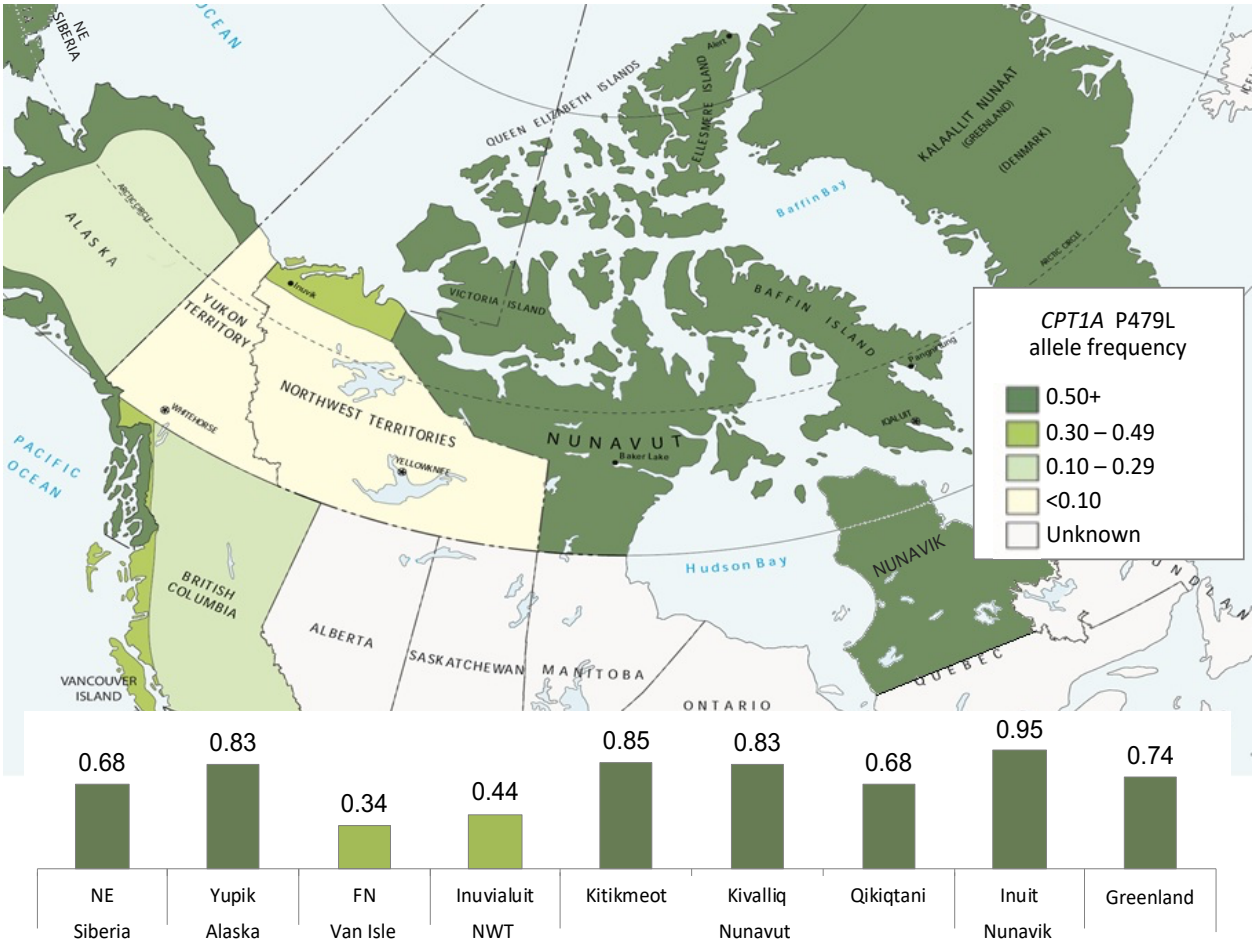

Figure 1.3 CPT1A p.P479L prevalence in arctic and coastal Indigenous populations
Allele frequencies for the p.P479L variant reported for northern coastal regions of Russia, Alaska, Canada and Greenland [17,20,22,117–119]. Map source: adapted from Full Details Reference Map of Canada obtained from Natural Resources Canada and contains information licensed under the Open Government Licence. © 2007. Her Majesty the Queen in Right of Canada, Natural Resources Canada [125].

The high prevalence of the p.P479L variant in Inuit populations combined with the evidence of positive selection for the variant suggests an historical advantage, allowing it to flourish and become the major allele [20,21,116,119]. The p.P479L variant follows the arctic coastal regions of Russia, Alaska, Canada and Greenland which are the traditional lands of the Inuit. The traditional diet of the Inuit (also known as country foods) consisted primarily of marine mammals (beluga and seal), fish and caribou, which were eaten cooked or raw and included skin, blubber and internal organs like liver, a diet very high in omega-3 fatty acids, moderate protein and very low carbohydrate [121,126]. The moderate insensitivity of the p.P479L variant to malonyl-CoA reported by Brown et al.[109] may have been historically advantageous to those living in the arctic, where the diet was primarily high in omega-3 fatty acids and little to no carbohydrate and continual fatty acid oxidation might be necessary for survival [14,119]. The traditional diet high in omega-3 fatty acids, combined with breastfeeding, would also increase hepatic *CPT1A* expression, possibly compensating for the decreased activity of the variant [20].

1.3.8.3 Evidence for positive health impacts

There is evidence that the p.P479L variant confers protection for adverse lipid profiles in adults, including increased HDL-cholesterol and apoA-I in adults. Rajakumar et al.[116] investigated variations in plasma lipid, lipoprotein and apolipoprotein levels profiles in Greenland Inuit (n=1,111, mean age 43.6$\pm$14.2 years) and found the p.P479L variant was associated with significantly higher plasma levels of HDL-cholesterol (HDL-C) and apoA-I; p.P479L homozygotes had mean HDL-C of 1.58mmol/L($\pm$0.02) and mean apoA-I of 1.78g/L($\pm$0.01), which indicates possible protection against atherosclerosis. Interestingly, p.P479L heterozygotes showed a significant intermediate increase in HDL cholesterol and apoA-I levels between non-

carriers and homozygotes [116]. Lemas et al.[118] reported similar results in a study of Alaska Yupik Eskimo individuals (n=1,141). The p.P479L variant was associated with lower adiposity and higher HDL-C after correcting for body mass index (BMI), percentage body fat (PBF) and waist circumference. The p.P479L variant has also been associated with lower height in Greenlanders (~2.1cm per allele copy), which may be due to differences in fatty acid metabolites and their role in growth hormone secretion [22].

1.3.8.4 Transitioning diet and the p.P479L variant

Recently, market foods that are high in processed carbohydrates have replaced many country (traditional) foods. Data from the 2007-2008 Inuit Health Survey shows a strong decline in country food use, suggests that energy dense market foods, which were mostly unavailable prior to the 1950's, now make up greater than 80% of the total diet energy for Inuit residing in Nunavut and only 11% of total diet energy comes from country foods for Inuit women of child bearing age (<40 years) and Inuit lactating women [127,128]. The study also report that the majority of dietary fat was derived from market foods with country foods contributing to 19% of PUFAs in diets of Nunavummiut, mostly from caribou and fish. Data from Kitikmeot reports that country food consumption may be slightly higher there, at 21% of total dietary energy [129].

Although the high prevalence of the p.P479L variant decreases the likelihood that homozygosity for the variant was deleterious historically, current dietary practices, with lower omega-3 fatty acids and higher carbohydrate rich foods, which would be expected to reduce hepatic *CPT1A* expression and activity [105,106], coupled with lower amount and length of breastfeeding

[126,130], may play a role in increasing risk for infants who might be affected with accompanying intercurrent illness.

1.3.8.5 Current evidence for association of p.P479L variant with early child health outcomes

Although there may have been an historical benefit with the variant and some evidence of protective effects in adulthood, there is concern that reduced enzyme activity could predispose infants and children with the p.P479L variant to hypoglycemia during prolonged fasting or illness and that reduced capacity for ketogenesis may result in metabolic decompensation during periods of infection. In addition, potential enzymatic instability of the variant might be unmasked with intercurrent illness, further exposing those who are homozygous for the variant to hypoglycemia, seizures, developmental delay and, in rare cases, sudden death. Under these circumstances, even for the mild condition, affected children might be dependent on the administration of glucose since their ability to utilize fats for energy production would be compromised.

There is evidence that some infants and children with the variant may present with features consistent with CPT1A deficiency. Greenberg et al.[14] described seven Canadian Inuit and BC First Nations children who came to clinical attention with features consistent with CPT1A deficiency. All patients were genotyped and found to be homozygous for the p.P479L variant; however, a number of apparently asymptomatic relatives were also determined to be homozygous for the variant [14].

To better understand outcomes for infants and children with the variant, Greenberg et al.[23] conducted a chart review of children from Kivalliq Nunavut, born between 2000 and 2006 (n=396; average age 5 years) to investigate the role of the p.P479L variant in seizure disorders. The overall prevalence of seizures in the chart review was 13% (febrile, afebrile and epilepsy). Children homozygous for the variant were significantly more likely to have experienced a seizure ($\chi2$=5.520, p=0.019, OR:2.51) and to have experienced afebrile seizures, whether epileptic or non-epileptic ($\chi2$=4.833, p=0.028, OR:7.12) [14]. All those diagnosed with epilepsy were homozygous for the variant, a proportion that fell just below statistical significance ($\chi2$=3.014, p=0.083, OR=+∞).

Further evidence came from Gillingham et al.[13], which studied fasting tolerance in five Alaska Native children homozygous for the variant (3-4years old). Of the five children enrolled in the study, two demonstrated abnormal fasting results during prolonged fasting and the fasting study had to be discontinued early at 16 hours. All five children had blunted ketone responses to fasting. These results suggest that there may be at least a sub-group of those infants and children homozygous for the variant unable to tolerate prolonged fasting, even without intercurrent illness. However, the two children that had abnormal fasting response had come to clinical attention for hypoglycemia prior to the study, so selection bias of study participants could not be ruled out. It remains unclear how the five participant children were ascertained in a population where ~800 infants homozygous for the variant are born each year, very few of whom come to attention clinically. In any case, the finding of a blunted ketone response to fasting in all five children is noteworthy.

1.3.8.6 CPT1A p.P479L and infectious disease

There is some evidence that the CPT1A p.P479L variant may contribute to the higher rates of infectious illness in populations where it is prevalent. To further understand the impact of the variant in morbidity in Alaska Native children, Gessner et al.[15] linked Alaska Medicaid administrative billing claims data to 427 Alaska Native children born in a three month period that had previously been genotyped by the Alaska Newborn screening program. The authors report that p.P479L homozygosity was associated with increased risk of otitis media (aOR:3.0, 95%CI:1.8-5.1), RSV (aOR:2.5, 95%CI:1.5-3.5), hospital admission for any reason (aOR:2.0, 95%CI:1.2-3.1) and hospital admission for LRTI (aOR:2.2, 95%CI:1.2-3.9), after adjusting for maternal education, age, prenatal smoking and alcohol use, prenatal care and birth weight. Children homozygous for the p.P479L variant were also younger at their first hospital admission and their first admission for LRTI.

The authors then analysed outcomes for 177 children in the Northern and Western non-hub villages which are inhabited primarily by Inupiat and Yupik people and where the variant is highly prevalent. In this subgroup, the association with otitis media remained significant (aOR:3.6, 95%CI:1.4-8.9) and there was a trend towards higher mean number of LRTIs compared to p.P479L heterozygotes. However, it is important to note that children not enrolled in Medicaid were excluded from the study and postnatal exposures and SES indicators were not included in the analysis.

In a more recent study, Sinclair et al.[18] used administrative medical services plan billing data of 150 BC First Nations children from British Columbia to investigate the risk associated with the CPT1A p.P479L variant. The study included an equal number of children of each genotype, 50 p.P479L homozygous, 50 p.P479L heterozygotes and 50 non-carriers. Children were residents of the same community and were matched for year of birth. The authors found that infants homozygous for the p.P479L variant were more likely to be admitted for LRTI (OR:6.0, 95%CI:1.6-22.4), otitis media (OR:13.5, 95%CI:1.5-109.4) and dental caries (OR:3.4, 95%CI:1.5-7.8) than those without the variant.. Added to this information is the recent evidence from Alaska reporting that homozygosity for the p.P479L variant was associated with increased risk for infant death due to infection illness in Alaska Natives [16].

1.3.8.7 Memory T cell survival and CPT1A

Infants and children with the CPT1A p.P479L variant may experience a more severe illness due to impaired ketogenesis and may also have impaired response of the immune system. CPT1A is important not only in the liver, but other tissues as well, including glucagon secretion in the pancreas [84], and the development and survival of some types of T cells [131–134]. A number of studies have demonstrated that CD8+ T memory (Tmem) cells and CD4+ Th17 and Treg cells have high demands for FAO and CPT1A activity [131–134]. Naïve T cells switch to glycolysis to support growth and differentiation into effector T-cells [135,136]. Once the infection is cleared, a small number of effector T-cells transition into long-lived Tmem cells, which rely for FAO and CPT1A activity for survival and rapid response to reinfection [137]. Enhanced FAO increases spare mitochondrial respiratory capacity (SRC) and the number of memory T cells generated [138–140].

Mouse model studies using both retroviral shRNAs to block *Cpt1a* and etomoxir, an irreversible inhibitor of CPT1A that binds the malonyl-CoA site, have found that CD8+ Tmem cells are reliant on FAO for cell survival and that Tmem cells expressed more *CPT1A* than T effector cells [134,141]. Additionally, retroviral mediated over-expression of *Cpt1a* increased the formation of Tmem cells but not Teff cells after *L. monocytogenes* infection [131], which indicates that FAO is part of the CD8+ T cell fate decision processes. Similarly, treatment of CD4+ naïve T cells with etomoxir reduces Treg induction/differentiation and Th17 development [142].

It is not known whether the CPT1A p.P479L variant impairs immune response and/or Tmem response to repeat infection; however, in a recent study exploring the connection between CPT1A blockade and multiple sclerosis (MS) Mørkholt et al.[143] found that the CPT1A p.P479L variant may affect the function of cells important in immunity. MS is an inflammatory demyelinating disease of the central nervous system (CNS) and a leading cause of neurological disability. The pathology of MS includes the infiltration of T cells and macrophages into the central nervous system. Recent studies have found that treatment with the CPT1A inhibitor etomoxir reduced inflammation, infiltration of macrophages and T cells in to the CNS, and demyelination of the CNS in mouse models of MS [144]. Interestingly, the rate of MS in the Greenlandic and Canadian Inuit is extremely low, which suggested a possible link to the CPT1A p.P479L variant [143,145]. Mørkholt et al.[143] used knock-in *Cpt1a* p.P479L homozygous mice to study the role of the variant in prevention of MS and found that the *Cpt1a* p.P479L mice were resistant to the induction of autoimmune encephalomyelitis (a mouse model of MS), suggesting the variant may confer protection through reduced lipid metabolism and/or reduced peripheral T cell infiltration and subsequent impaired immune system activation [143].

1.3.8.8 p.P479L variant and infant death

Nunavut has the highest rate of SIDS, SUDI and infant death due to infection in Canada. In my review of infant mortality in Nunavut for infants born from 1999 to 2011 [12], I found that homozygosity for the p.P479L variant was associated with increased risk for SIDS, SUDI and death due to infection (OR:3.4, 95%CI:1.3-11.5). The results were consistent with those of Sinclair et al.[17] which reported an over-representation of p.P479L homozygotes in SIDS, SUDI and death due to infection cases in BC First Nations infants less than two years of age (OR 3.9, 95%CI:1.7–9.0). In 2016, Gessner et al.[16] reported that p.P479L homozygosity was associated with infant deaths due to infection in Alaska Natives (OR: 2.9, 95%CI:1.0-8.0). Interestingly, the association with SIDS and SUDI was not significant in that study (OR:1.08, 95%CI 0.55-2.11).

A number of genetic factors have been identified that may increase the risk for SIDS and SUDI, which include factors associated with neural control of respiratory function [146–152] and gene variants that cause metabolic disorders; undiagnosed fatty acid oxidation disorders leading to undetected hypoketotic hypoglycaemia may account for up to 3-6% of SIDS and SUDI cases [70,72,73], which has raised concerns that the CPT1A p.P479L variant combined with prolonged fasting or intercurrent illness, could increase risk of sudden death as an effect of hypoglycaemia, perhaps in combination with prone sleeping, where sleep is deeper [12].

1.3.8.9 Newborn screening and the CPT1A p.P479L variant

Since infants homozygous for the variant commonly have higher CPT1A activity levels than those with classic CPT1A deficiency, only a small percentage are identified using standard cut-offs [17]. Sinclair et al.[17] found that lowering the C0/C16+C18 cut-off from 100 to 14 has high sensitivity (94%) for detecting those homozygous for the variant, but also a high false positive rate (6%). In Alaska, newborns are directly tested for the p.P479L variant of CPT1A. In Canada, classic CPT1A deficiency screening is included in NBS programs in Manitoba and Ontario, but not Alberta. The potential merits of NBS for the p.P479L variant was discussed at the Garrod Society Meetings (May 2015). Given the outstanding questions regarding the penetrance of the variant and determining which infants are at risk for adverse health outcomes, there was a national consensus that there is insufficient data to support screening at this time. It was unclear whether identifying all infants with the variant through a more precise method would result in effective management strategies for what may be a 'susceptibility' factor.

1.4 GAPS IN KNOWLEDGE

Why infants homozygous for the p.P479L variant higher rates of infectious illness is not known. It is possible that variants in CPT1A may not only impair ketogenesis in the liver but also glucagon secretion from pancreatic alpha cells in response to low blood glucose levels, further reducing the amount of liver gluconeogenesis and ketogenesis, which would impair homeostatic response to intercurrent illness. CPT1A is also important in memory T cell development and survival [131,132,134], raising questions regarding the lower activity level of the p.P479L variant and its possible impact on immune function and response. Although this is suggestive, the underlying aetiology of the link between infectious disease and the p.P479L variant remains

unknown at this time. There are high rates of risk factors associated with infectious illness in early childhood in Nunavut, including tobacco smoke exposure [30,46], household crowding [47], food insecurity in young children in Nunavut [32] and lower rates of breastfeeding initiation compared to the national averages [153]. How these issues may affect the biological effect of the p.P479L variant remains unclear.

1.5 DISSERTATION OVERVIEW

Understanding how a variant with apparent historical advantage might also confer susceptibility to adverse childhood health outcomes has remained controversial. The p.P479L variant has been identified as a deleterious variant of CPT1A, associated with a number of adverse infant and child health outcomes, but also has the strongest signal of positive selection ever reported for humans [119], creating uncertainty regarding the clinical significance of the variant in infant and child health. There have been calls for more comprehensive study on the impact of the p.P479L variant to determine if the previously reported associations of the variant with adverse infant and child health outcomes are independent of those socioeconomic status (SES) and other indicators common in these populations that were not assessed in previous studies [154].

This dissertation assesses the impact of CPT1A p.P479L variant on Inuit infant and child health in the context of information collected through clinical chart review and investigates the association of the p.P479L variant with those outcomes in the broader context of SES and other characteristics prevalent in the population. The dissertation uses infant and early child health outcomes data for Inuit children in Nunavut born from January 1st, 2010 to December 31st, 2013, based on a comprehensive chart review in 18 of the 25 Nunavut communities, including all

communities with greater than 20 births per year. The data for the study was collected over a two- and half-year period from June 2016 to January 2019 and is the largest population study of Inuit child health conducted in Nunavut to date.

Three separate but overlapping papers are presented that complete the dissertation, one which has been published, and the other two are in the process of submission. In the first paper (Chapter 2), I explore the current status of infant and child health in Nunavut and examine the variation of outcomes and exposures across the territory's three regions, including rates of admissions for respiratory tract infections and other important early child health outcomes along with important maternal and postnatal characteristics associated with those outcomes. My findings confirm that rates of infectious illness in infancy and early childhood remain high in Inuit children in Nunavut and the risk factors of household crowding, food insecurity and maternal smoking remain high. I also found evidence of encouraging trends that might have a positive impact on health including high rates for breastfeeding initiation and duration for infants residing with their biological mothers and country food use in children aged two to five years of age. The results of this chapter provide critical background information for my risk analysis of adverse child health outcomes associated with the CPT1A p.P479L variant.

In the second paper (Chapter 3), I determined that neonatal hypoglycemia is higher than expected in healthy term Inuit newborns with no risk factors for hypoglycemia and that newborns with the p.P479L variant (both homozygous and heterozygous) have higher incidences of neonatal hypoglycemia than newborns without the variant. Finally, in the third paper (Chapter 4), I determined that the p.P479L variant of CPT1A was associated with infectious illness in

infancy and early childhood in Inuit children of Nunavut. This association was independent of breastfeeding, postnatal maternal smoking, food security and community level socioeconomic status, which includes measures of income, education and household crowding. These two papers also provide support that there may be a heterozygous effect of the p.P479L allele, an effect that has previously not been well delineated.

I summarise my findings in Chapter 5 placing them into context of what is known and what still needs to be determined about the impact of the CPT1A p.P479L variant, with suggestions for future studies that could help to close those gaps. This study is the first, large and comprehensive population-based study to assess the risk associated with this unique variant and addresses many of the outstanding concerns around the potentially confounding factors of SES and other indicators common in these populations. The findings of this research provide a comprehensive view of the infant and child morbidity in Nunavut which can be used to inform policies that address and reduce child health disparity in the territory.

CHAPTER 2. THE CURRENT STATUS OF THE HEALTH OF INUIT INFANTS AND CHILDREN OF NUNAVUT (PAPER 1)

2.1 INTRODUCTION

Nunavut is Canada's largest jurisdictional landmass, with 25 remote communities along the arctic coastline and 39,000 inhabitants, called Nunavummiut, of which 85% self-identify as Inuit [1,2] with unique socio-cultural strengths and perspectives. The territory lies above the arctic tree line and is only accessible by air or sea, requiring all food to be shipped by plane. There are numerous challenges for health and health care delivery, and, as such, the health status of Inuit children has garnered attention and concern for several decades [3–5]. Inuit children living in Nunavut have been reported to have the highest national rates of prematurity (14%, <37weeks gestation) [24], congenital anomalies [28,50], infant admissions for lower respiratory tract infection (LRTI; 234-306/1,000 live births) [4,6] and infant mortality (21.5/1000) [9]. The leading causes of post-neonatal infant mortality in Nunavut are sudden infant death syndrome and sudden unexpected death in infancy (SIDS/SUDI) and death due to infection (1999-2011) [12]. Early child health in Nunavut is influenced by a number of perinatal, postnatal and socioeconomic indicators, including environmental and household socioeconomic characteristics including household crowding, food insecurity and tobacco smoke exposure [6,10,46,74].

Nunavut has the largest Inuit population in Canada [155]; approximately 850 infants are born to Nunavut residents (Nunavummiut) each year [26]; 90% to Inuit women [2,36]. Medical care in Nunavut largely relies on nurse run health centres in the remote communities of Nunavut's three regions, Qikiqtaaluk, Kivalliq and Kitikmeot (Figure 2.1). Secondary care is provided at the

Iqaluit General Hospital for residents of Qikiqtaaluk. Residents in the other regions travel to surrounding provinces for secondary care. Specialist care may be delivered by traveling clinics, or travel to tertiary centres [37,38]. Within Nunavut, births occur at the Qikiqtani General Hospital or at low-risk midwife birthing centres in Cambridge Bay and Rankin Inlet. An average of 50% of births to Nunavummiut occur out of territory in surrounding provinces [26].

A number of studies have reported high rates of adverse child health outcomes for Inuit children in Nunavut [3–5,12,50,53]. To better understand and improve child health outcomes for Nunavummiut, Lauson et al.[156] described the development of a comprehensive maternal child health information system, which included a diverse group of professional and lay stakeholders to determine the key prenatal, perinatal and early child health variables important for understanding maternal and child health outcomes in Nunavut. As part of the project, prenatal, labour/deliver and well-baby records were modified to include Nunavut-specific variables of nutrition, food security, exposures in pregnancy, congenital anomalies, development and chronic diseases of childhood. Lauson et al. also provided a review of current evidence for adverse child health outcomes and risk factors in Nunavut. Although the program was discontinued, the process and forms developed are an important resource for understanding maternal child health in Nunavut.

This study reports on the results of a comprehensive retrospective chart review of Inuit infants born between 2010 and 2013 that included the modified Nunavut-specific forms developed for the health information system and provides an update on the recent status of the health of Inuit infants and children of Nunavut.

Figure 2.1 Regions of Nunavut Canada
Red dots indicate communities. Red star indicates territorial capital, Iqaluit. Compiled by Chris Kalluk, Nunavut Tunngavik Incorporated; using Data from Atlas of Canada and the National Topographic Data Base (NTDB)

2.2 METHODS

2.2.1 Research ethics

As part of a larger study, ethics approval was granted by the University of British Columbia and University of Victoria Research Ethics Boards, and a research licence was granted by the Nunavut Research Institute. The study was developed and conducted in partnership with the Government of Nunavut Department of Health, Nunavut Tunngavik Inc. (NTI) and the

Qaujigiartiit Health Research Centre (QHRC). NTI is responsible for ensuring the implementation of and adherence to the Nunavut Land Claims Agreement and advocates for policies and programs that enhance Inuit well-being, which includes healthy children. The QHRC is a community-led research institute that fosters local leadership and engagement in research activities involving the health and well-being of Nunavummiut.

2.2.2 Chart review

Well-child and clinic charts of children born to mothers residing in Nunavut from 01-Jan-2010 to 31-Dec-2013 were reviewed at community health centres, Iqaluit Public Health and the general hospital in Iqaluit. All communities with more than 20 births/year (18/25 communities) were visited for chart review. A total of 2691 charts were reviewed, 577 charts in Kitikmeot (5/5 communities), 821 charts in Kivalliq (6/7 communities) and 1293 charts in Qikiqtaaluk (7/13 communities) representing 80% of the 3400 births reported for Nunavut by Statistics Canada for the time period [26]. Charts for non-Inuit children (n=169) were excluded leaving a final cohort of 2523 Inuit children in the study (94% of charts reviewed).

Chart reviewers abstracted medical data from physical paper charts in health centres and Iqaluit Public Health or from electronic medical charts at the Qikiqtani General Hospital. Data included prenatal, labour/delivery, newborn and well-baby records and clinical charts until five years of age. Information collected encompassed birth data (e.g. gestational age, birth weight, length and head circumference, place and type of birth, plurality (singleton or multiple birth), perinatal and postnatal exposures (including periconceptional vitamin use (three months prior to pregnancy), prenatal vitamin use and smoking), breastfeeding initiation, well baby visit information (Figures

A.1.1-6, Sub-Appendix A.1). For health centre visits and emergency room visits (Iqaluit only), data abstracted included: reason for visit, treatments and outcomes, medical diagnoses (infectious disease, congenital anomalies, anemia etc.), and whether medical evacuation or hospital admission (Iqaluit) was required. For hospital admissions, data abstracted included: reason for admission (primary and secondary reasons), length of admission, tests and treatments administered and medical diagnoses (infectious disease, congenital anomalies, anemia etc.). Inuit ethnicity was determined using mother's and/or infant's ancestry indicated on the chart. Custom adoption is a traditional cultural practice of adoption and caretaking in Indigenous communities and is common in Nunavut [29,157] and was collected to allow analysis of breastfeeding of children without documented custom adoption. Upon completion of the chart review, duplicate records (records for children in more than one location) were merged into one record.

Housing, country food and food security data were collected as recorded on the well-baby forms for 2, 6, 12, 24, and 48-month visits (Figures A.1.1-5, Sub-Appendix A.1). Well baby records are completed by nurses at community health centres or Iqaluit Public Health during the well-baby visits based on nurse assessments as well as answers provided by the primary caregiver at the visit. Housing was measured using the number of people living in the home and the number of bedrooms in the home. Country food (sometimes also called traditional food) use was collected as recorded on Nunavut well-baby forms for 24- and 48-month visits. In Nunavut, country foods include beluga and seal, fish and caribou [121,126]. Food insecurity was defined using the primary caregiver answer to the question "since your baby was born/your last visit, were there times when the food for you and your family just did not last and there was no money to buy

enough food?" Answers of 'Often' or 'Sometimes' were combined as yes, 'No/Never' were categorized as no and 'Don't know/refused' as missing.

2.2.3 Outcome measures

Primary birth outcomes were preterm birth (<37 weeks gestation), low birth weight (<2500g), high birth weight (HBW, >4500g), small for gestational age (SGA, <10th percentile), large for gestational age (LGA, >90th percentile), congenital anomalies detected by one year of age, infant death (0-364days), neonatal death (0-27days) and post-neonatal death (28-364 days). Size for gestational age was calculated using the WHO Growth Charts for Canada [158]. Minor structural anomalies, anomalies that self-resolved in the first three months of life, and anomalies related to prematurity were excluded from counts. Causes of death were categorised into five categories: sudden infant death syndrome and sudden unexpected death in infancy (SIDS/SUDI), congenital anomalies, prematurity, infection and other.

Primary early child health outcomes were LRTI, respiratory syncytial virus (RSV) infection, admission to regional or tertiary hospital (>24hrs) for LRTI, admission to hospital with RSV (>24hrs), otitis media (middle ear infections), gastroenteritis (vomiting and/or diarrhea not otherwise explained), tuberculosis and anemia (hemoglobin <11g/dL). Repeat visits or admissions within 14 days of initial visit/admission were not counted. Records excluded from early child health outcome analysis were those charts with limited data and/or missing medical history (e.g. missing chart, charts with a single visit to health centre, or charts with newborn data only; n=60), leaving 2463 records with medical data.

2.2.4 Statistical analysis

Proportions of preterm birth, LBW, HBW, SGA, LGA were calculated per 100 births with data for that variable. Rates for congenital anomalies and infant mortality were calculated per 1,000 infants reviewed (n=2523). Rates and proportion for early child health outcomes were calculated per 1000 or 100 infants (respectively) with medical data (n=2463). Descriptive statistics were used to summarize differences in covariates and outcomes by region and used univariable logistic regression to compare outcomes in Kivalliq and Kitikmeot regions to the Qikiqtaaluk region, which is the only region with a hospital. Odds ratios with 95% confidence intervals were considered statistically significant for two-tailed p-values<0.05. All data were analyzed using Stata 16SE [159].

2.3 RESULTS

There were 2523 Inuit children included in the review. The majority resided in Qikiqtaaluk (n=1149), followed by Kivalliq (n=805) and Kitikmeot (n=569). The proportion of infants born premature was 15.4%, ranging from 12.7% in Kitikmeot to 17.2% in Kivalliq (Table 2.1). Low birth weight was recorded for 8.5% of births (<2500g). SGA births ranged from 5.5% in Qikiqtaaluk to 6.7% in Kitikmeot. The majority of births were spontaneous vaginal deliveries (84.1%), 7.1% of births occurred by caesarean section, which was lowest in the Kivalliq region at 5.8%.

There were 233 congenital anomalies documented in 183 infants in the cohort, 34 infants had two or more congenital anomalies. The rate of congenital anomalies for Nunavut as a whole was 92.4/1,000 Inuit infants; 90.6/1,000 in Kivalliq , 91.4/1,000 in Kitikmeot and 94.1/1,000 in

Qikiqtaaluk. The infant mortality rate for the cohort was 19.8/1,000 infants (n=50, Figure 2.2). The leading cause of infant death was Sudden Infant Death Syndrome and Sudden Unexpected Death in Infancy (SIDS/SUDI), with a mortality rate of 9.1/1,000 infants (n=23, Table 2.2).

Table 2.1 Infant and maternal characteristics by region for Inuit children Nunavut (2010-2013)

	Nunavut		**Qikiqtaaluk**		**Kivalliq**		**Kitikmeot**		**Missing**
	n	**(%/rate)[a]**	**n**	**(%/rate)[a]**	**n**	**(%/rate)[a]**	**n**	**(%/rate)[a]**	
Births reviewed	2523		1148		806		569		
Singleton	2473/2523	(98.0)	1131/1148	(98.4)	781/806	(97.0)	560/569	(98.6)	
Male	1269/2516	(50.4)	582/1144	(50.9)	413/804	(51.4)	274/568	(48.2)	0.3%
Preterm (<37wks)	377/2451	(15.4)	171/1104	(15.5)	135/787	(17.2)	71/560	(12.7)	2.8%
SGA (<10th)	143/2406	(5.9)	60/1089	(5.5)	46/762	(6.0)	37/555	(6.7)	4.6%
LGA (>90th)	334/2406	(13.9)	159/1089	(14.6)	87/762	(11.4)	88/555	(15.9)	
LBW (<2500g)	209/2447	(8.5)	94/1112	(8.5)	63/772	(8.2)	52/563	(9.2)	3.0%
HBW (>4500g)	41/2447	(1.7)	21/1112	(1.9)	7/772	(0.9)	13/563	(2.3)	
Delivery: SVD	1985/2361	(84.1)	904/1094	(82.6)	682/739	(92.3)	399/528	(75.6)	6.4%
Delivery: CS	168/2361	(7.1)	85/1094	(7.8)	43/739	(5.8)	40/528	(7.6)	
Congenital anomalies	233/2523	(92.4)	108/1148	(94.1)	73/806	(90.6)	52/569	(91.4)	
Infant death	49/2523	(19.8)	27/1148	(23.5)	16/806	(19.9)	7/569	(12.3)	

[a]Proportions for male sex, preterm, SGA, LGA, LBW, HBW calculated per 100 births with data for variable. Rates of total number of congenital anomalies and infant death calculated per 1,000 births reviewed. Preterm: preterm birth (<37weeks gestation), SGA: small for gestational age (10th percentile), LGA: large for gestational age (>90th percentile), LBW: low birth weight (<2500g), HBW: high birth weight (>4500g), SVD: spontaneous vaginal delivery, CS: Caesarean section delivery

Table 2.2 Rates of infant death by cause of death for Inuit infants in Nunavut (2010-2013)

	n	Rate (95%CI)
Live births	2523	
Infant death (0-364days)	50	19.8 (15.0-26.6)
Neonatal death (0-27days)	15	5.9 (3.4-9.8)
Post-neonatal death (28-364days)	35	13.9 (9.8-19.5)
Cause of Death		
SIDS and SUDI	23	9.1 (5.8-13.8)
Prematurity	11	4.4 (2.2-7.8)
Congenital anomalies	11	4.4 (2.2-7.8)
Infection	6	2.4 (0.9-5.2)
Other causes	6	2.4 (0.9-5.2)

Rates calculated per 1,000 Inuit infants (n=2523). SIDS: Sudden Infant Death Syndrome, SUDI: sudden unexpected death in infancy.

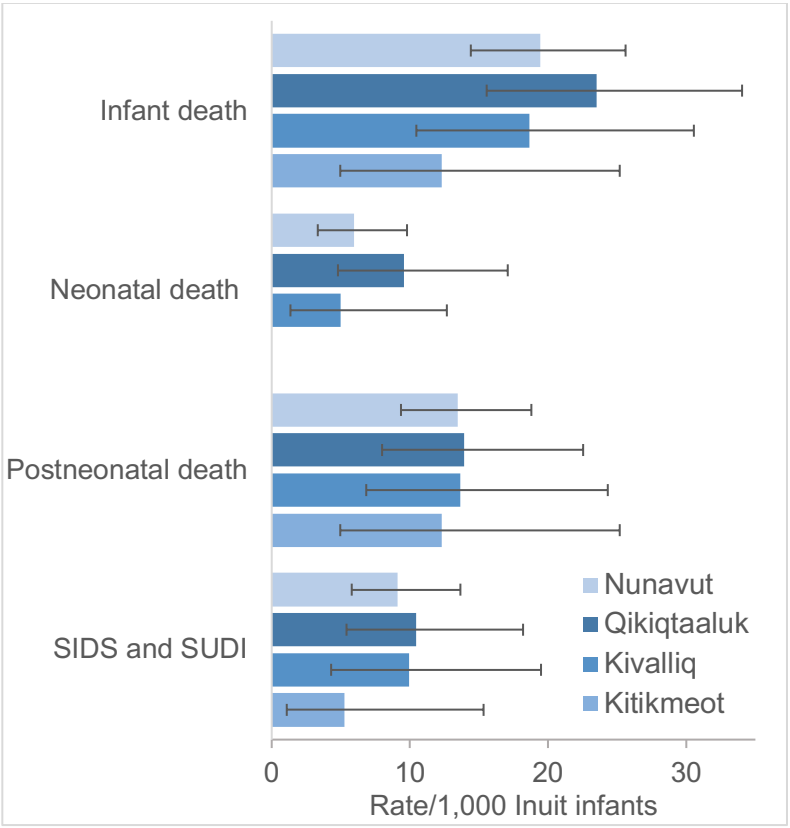

Figure 2.2 Rates of infant death by region for Inuit infants in Nunavut (2010-2013, n=2523)

2.3.1 Maternal and postnatal characteristics

Mean maternal age was 24 years and 22.4% of women were under 20 years of age (Table 2.3). Seventeen percent of women reported taking multi, prenatal and/or folic acid vitamins in the periconceptional period and 70% reported taking prenatal vitamins and/or folic acid during pregnancy. Prenatal anemia was documented for 35.9% of women and ranged from 26.1% in Kivalliq to 50.3% in Kitikmeot.

Breastfeeding initiation was reported for 74.0% of children. One in three women breastfed for six months (35.2%) or longer and 27.1% breastfed for 12 months or longer. Breastfeeding initiation and duration were highest in Qikiqtaaluk, 78.2% of women initiated breastfeeding, 41.6% reported breastfeeding for six months or longer and 32.8% for 12 months or longer. Custom adoption was documented in 20.4% charts in the cohort (n=514); when those charts were excluded from analysis, 86.3% (1586/1839) of women initiated breastfeeding, 42.7% reporting breastfeeding for six months or longer and 33.1% for 12 months or longer.

The majority of women reported smoking during pregnancy, 84.1% were active smokers during pregnancy and 85.6% were active smokers after pregnancy. During pregnancy, 34.5% (722/2093) of women reported not smoking or smoking less than 5 cigarettes per day and 31.2% (629/2016) of women reported not smoking or smoking less than 5 cigarettes per day after pregnancy. Heavy smoking (≥10cig/day) was reported in 13.7% of pregnancies and 16.6% of women reported heavy smoking after pregnancy.

Table 2.3 Maternal and household characteristics by region for Inuit children in Nunavut, 2010-2013

	Nunavut n (%)	Qikiqtaaluk n (%)	Kivalliq n (%)	Kitikmeot n (%)	Missing %
Births	2523	1148	806	569	
Mat age <20yrs[a]	514/2297 (22.4)	211/1015 (20.8)	175/750 (23.1)	128/522 (24.5)	9.0
mean mat age	24.1 yrs	24.6 yrs	23.8 yrs	23.7 yrs	
Periconcep vit[b]	253/1488 (17.0)	120/593 (20.2)	94/520 (18.1)	39/375 (10.4)	41.0
Prenatal vits[c]	1065/1519 (70.1)	412/607 (67.9)	348/524 (66.4)	305/388 (78.6)	39.8
Prenatal anemia	824/2295 (35.9)	362/1013 (35.7)	197/755 (26.1)	265/527 (50.3)	9.9
Mat. diabetes[d]	51 (2.2)	28 (2.8)	15 (2.0)	8 (1.5)	
Mat. HTN[e]	139 (6.1)	43 (4.2)	61 (8.1)	35 (6.6)	
Preeclampsia/eclampsia	41 (1.8)	28 (2.8)	5 (0.7)	10 (1.9)	
Prenatal cholestasis	26 (1.1)	6 (0.6)	9 (1.2)	11 (2.1)	
Prenatal smoking	1760/2093 (84.1)	745/886 (84.1)	610/716 (85.2)	405/491 (82.5)	17.0
Light (1-4pd)	389 (18.6)	147 (16.6)	117 (16.3)	125 (25.5)	
Mod.(5-10pd)	822 (39.3)	345 (38.9)	269 (37.6)	208 (42.4)	
Heavy (>10pd)	286 (13.7)	138 (15.6)	118 (16.5)	30 (6.1)	
Amt unknown	263 (12.6)	115 (13.0)	106 (14.8)	42 (8.6)	
Postnatal mat. smk	1726/2016 (85.6)	839/967 (86.8)	493/573 (86.0)	394/476 (82.8)	20.1
Light (1-4pd)	339 (16.8)	156 (16.1)	84 (14.7)	99 (20.8)	
Mod (5-10pd)	944 (46.8)	453 (46.9)	264 (46.1)	227 (47.7)	
Heavy (>10pd)	334 (16.6)	173 (17.9)	123 (21.5)	38 (8.0)	
Amt unknown	109 (5.4)	57 (5.9)	22 (3.9)	30 (6.3)	
BF initiation	1708/2309 (74.0)	842/1077 (78.2)	448/694 (64.6)	418/538 (77.7)	8.5
BF ≥6mths	812 (35.2)	448 (41.6)	182 (26.2)	182 (33.8)	
BF ≥12mths	625 (27.1)	353 (32.8)	137 (19.7)	135 (25.1)	
BF initiation (excl. adopt)[f]	1586/1839 (86.2)	800/880 (90.9)	399/515 (77.5)	387/444 (87.2)	
BF ≥6mths	785 (42.7)	440 (50.0)	170 (33.0)	175 (39.4)	
BF ≥12mths	608 (33.1)	348 (39.5)	129 (25.0)	131 (29.5)	
Country food use (2-5yrs)	1279/1337 (95.7)	661/699 (94.6)	394/407 (96.8)	224/231 (97.0)	47.0
Daily or more	434 (32.5)	184 (26.3)	153 (37.6)	97 (42.0)	
≥Once/week	567 (42.4)	322 (46.1)	158 (38.8)	87 (37.7)	
Food insecurity	828/1961 (42.2)	455/960 (47.4)	207/546 (37.9)	166/455 (36.5)	22.2
Housing: >2 ppl/bedroom[g]	958/1884 (50.9)	464/933 (49.7)	273/504 (54.2)	221/447 (49.4)	25.3
>3 ppl/bedroom	344 (18.2)	148 (15.8)	120 (23.7)	76 (16.9)	
mean ppl in home	6.0 ppl	6.0 ppl	6.1 ppl	5.8 ppl	

[a]Proportions calculated per 100 births with data for variable. [a]Mat age: Maternal age, [b]Periconceptional vit: multi or prenatal vitamins and/or folic acid. [c]Prenatal vit: Prenatal vitamin and/or folic acid. [d]Maternal DM: maternal diabetes, pre-existing or gestational, [e]Maternal hypertension without preeclampsia. [f]Breastfeeding after excluding records with documented custom adoption (n=514). [g]Housing: number of people living in the home divided by the number of bedrooms in the home.

Three out of four children (1001/1337) ate country food at least once a week, and 32.5% ate country food daily. Country food use was similar across the regions, but daily consumption was highest in Kitikmeot (42.0%). Food insecurity was reported for 42.2% of children, ranging from 36.5% in Kitikmeot to 47.4% in Qikiqtaaluk. There was a mean of six people living in a single home, which did not vary between regions, and 50.9% of children lived in homes with more than two people per bedroom, 49.4% in Kitikmeot, 49.7% in Qikiqtaaluk and 54.2% in Kivalliq.

2.3.2 Early child health outcomes

LRTI was documented for 74.3% of children under the age of five and 28.0% of children were admitted for LRTI (regional or tertiary hospital care; Table 2.4). There was a total of 1084 admissions for LRTI; the mean number of admissions was per child was 0.4 (range 0-9). RSV testing was documented for 42.7% (463/1084) of LRTI admissions and 226 cases tested positive, for a child RSV admission rate of 91.8/1,000. Child admissions with RSV were significantly lower in Kivalliq (OR:0.53, 95%CI:0.36-0.77); however, Kivalliq had the lowest documented RSV testing at 24.3%.

Just over half of children (57.6%) had LRTI at least once during infancy and there was a total of 726 admissions of 516 infants for LRTI. The rate of infant admission for LRTI was 294.8/1000 infants for Nunavut, ranging from 273.8/1,000 in Qikiqtaaluk, 275.0/1,000 in Kivalliq and 364.3/1,000 in Kitikmeot. Infants from Kitikmeot were more likely to be admitted for LRTI (OR:1.41, 95%CI:1.11-1.80) than those in Qikiqtaaluk. RSV testing was documented for 48.8% (354/726) of infant admission for LRTI and 177 cases tested positive. Documented RSV testing ranged from 29.5% in Kivalliq, 53.4% in Qikiqtaaluk and 62.3% in Kitikmeot.

Table 2.4 Infant and child health outcomes by region for Inuit children in Nunavut, 2010-2013

	Nunavut n (%/rate)	Qikiqtaaluk n (%/rate)	Kivalliq n (%/rate)	Kitikmeot n (%/rate)	Kivalliq vs Qikiqtaaluk OR (95%CI)	p	Kitikmeot vs Qikiqtaaluk OR (95%CI)	p
Charts with health data	2463	1115	789	559				
LRTI, 0-5yrs	1829 (74.3)	794 (71.2)	577 (73.1)	458 (82.9)	1.10 (0.90-1.34)	0.358	1.83 (1.43-2.36)	<0.001
Children admitted for LRTI	689 (28.0)	308 (27.6)	217 (27.5)	164 (29.3)	0.99 (0.81-1.22)	0.954	1.09 (0.87-1.36)	0.462
LRTI admission rate /1000	1084 (440.1)	484 (434.1)	321 (406.8)	279(499.9)				
Admits tested for RSV	463 (42.7)	230 (47.5)	78 (24.3)	155 (55.6)				
RSV, 0-5yrs	391 (15.9)	178 (15.9)	83 (10.5)	130 (23.2)	0.62 (0.47-0.82)	0.001	1.59 (1.24-2.05)	<0.001
Children admitted with RSV	206 (8.4)	103 (9.2)	40 (5.1)	63 (11.3)	0.53 (0.36-0.77)	0.001	1.25 (0.90-1.74)	0.186
RSV admission rate/1000	226 (91.8)	116 (104.0)	45 (57.0)	65 (116.1)				
LRTI, Infants (<1yr)	1419 (57.6)	593 (53.1)	462 (58.6)	364 (65.0)	1.24 (1.03-1.48)	0.025	1.62 (1.32-2.00)	<0.001
Infants admitted for LRTI	516 (21.0)	210 (18.8)	168 (21.3)	138 (24.7)	1.17 (0.86-1.30)	0.185	1.41 (1.11-1.80)	0.006
LRTI admission rate /1000	726 (294.8)	305 (273.8)	217 (275.0)	204 (364.3)				
Admits tested for RSV	354 (48.8)	163 (53.4)	64 (29.5)	127 (62.3)				
RSV, Infants (<1yr)	289 (11.7)	121 (10.8)	69 (8.7)	99 (17.7)	0.79 (0.58-1.08)	0.135	1.77 (1.33-2.36)	<0.001
Infants admitted with RSV	169 (6.9)	76 (6.8)	37 (4.7)	56 (10.0)	0.68 (0.46-1.02)	0.065	1.55 (1.08-2.22)	0.018
RSV admission rate/1000	177 (71.8)	80 (71.6)	40 (50.7)	57 (101.8)				
Otitis media, 0-5yrs	2,109 (85.6)	893 (79.9)	678 (85.9)	538 (96.1)	1.53 (1.20-1.96)	0.001	6.43 (4.06-10.18)	<0.001
Children with ≥3 episodes	1412 (57.3)	537 (48.1)	438 (55.5)	437 (78.0)	1.35 (1.12-1.62)	0.001	3.84 (3.04-4.84)	<0.001
Otitis media, Infants (<1yr)	1,538 (62.4)	618 (55.3)	480 (60.8)	440 (78.6)	1.25 (1.04-1.51)	0.017	2.99 (2.36-3.77)	<0.001
Gastroenteritis, 0-5yrs	1,231 (49.9)	620 (55.5)	283 (35.9)	328 (58.6)	0.45 (0.37-0.54)	<0.001	1.14 (0.93-1.40)	0.217
Gastroenteritis, Infants (<1yr)	703 (28.5)	360 (32.2)	156 (19.8)	187 (33.4)	0.52 (0.42-0.64)	<0.001	1.06 (0.85-1.31)	0.615
Anemia, 0-5yrs	1382 (56.1)	606 (54.4)	473 (60.0)	303 (54.1)	1.25 (1.04-1.51)	0.016	0.99 (0.81-1.21)	0.910

Proportions calculated per 100 children (n=2463). Rates of total number of LRTI and RSV admissions were calculated per 1,000 children (n=2463). Outcomes for Kivalliq and Kitikmeot regions are compared to the Qikiqtaaluk region, which is the region with a hospital. CI: confidence interval, LRTI: lower respiratory tract infection. OR: odds ratio, RSV: respiratory syncytial virus.

The rates of infant admission with RSV in each region were 50.7/1,000 in Kivalliq (n=40), 71.6/1,000 in Qikiqtaaluk (n=80) and 101.8/1,000 in Kitikmeot (n=57), with an overall rate of 71.9/1,000 infants for the territory. Infant admissions with RSV were significantly higher in Kitikmeot (OR:1.55, 95%CI:1.08-2.22). The rate of infant admissions with RSV varied by birth year and was highest for infants born in 2011 (80.8/1,000) and lowest for infants born in 2012 (63.4/1,000; Table 2.5).

Table 2.5 Admissions with RSV in Inuit infants in Nunavut, by birth year

Birth Year	**Infants reviewed**	**Infants Admitted**		**Total Admissions**	
		n	**%**	**n**	**rate***
Total	2463	168	(6.8%)	177	(71.8)
2010	639	45	(7.0%)	47	(71.4)
2011	618	48	(7.8%)	51	(80.8)
2012	567	36	(6.4%)	37	(63.4)
2013	639	40	(6.3%)	42	(64.7)

Rate: per 1,000 Inuit infants reviewed , RSV: respiratory syncytial virus

Otitis media was documented for 2109 children (85.6%), 1538 children (62.4%) had a diagnosis of otitis media before one year of age and 1412 children (57.3%) had three or more episodes of otitis media by the age of five. Otitis media was significantly higher in Kivalliq (OR:1.53, 95%CI:1.2-1.96) and Kitikmeot (OR:6.43, 95%CI:4.06-10.18) compared to Qikiqtaaluk. Most occurrences of otitis media were acute (AOM); however, 13.2% of children were reported to have chronic otitis media (COM), 25.6% had otitis media with draining ears and 5.5% otitis media with reported effusion. Six percent of children required ear tube insertion and 15% of children had documented tympanic membrane perforation.

Half of all children had at least one episode of gastroenteritis and 28.5% had gastroenteritis during infancy. Children living in Kivalliq were less likely to have gastroenteritis (OR:0.45, 95%CI:0.37-0.54) than children in Qikiqtaaluk. Tuberculosis treatment was documented for 146 children (18 active tuberculosis and 128 latent tuberculosis). The majority of cases resided in Qikiqtaaluk, accounting for 11.9% (137/1148) of the cohort living in the region.

Anemia was documented in 56.1% of children, ranging from 54% in Qikiqtaaluk and Kitikmeot to 60.0% in Kivalliq. Children in Kivalliq were more likely to have anemia (OR:1.25, 95%CI:1.04-1.51) compared to Qikiqtaaluk. However, iron deficiency anemia was reported in only 2.1% of the cohort.

2.4 DISCUSSION

The health outcomes for Inuit infants and children has been a focus of public health research for several decades [5,156]. Previous research has shown elevated rates of prematurity, congenital anomalies, infectious illness and infant death in Canadian Inuit populations, including in Nunavut [3–5,12,50,53]. Here I present the largest and most comprehensive assessment of Inuit infant and child health status assessment of Nunavut to date, which was carried out in all three regions and included greater than 80% of births during the study period. The results of this study corroborate previous studies that rates of prematurity, congenital anomalies, infant mortality and infectious illness remain high in Inuit children living in Nunavut.

2.4.1 Congenital anomalies

The rate of congenital anomalies reported here (92.7/1,000 infants) is similar to that of a baseline chart review of 2567 Inuit infants born from 1989-1994 to Inuit women residing in Arctic Quebec (Nunavik) and Qikiqtaaluk Nunavut reported a congenital anomaly rate of 93.1/1000, which was twice the rate reported by the Canadian provincial birth defect registry, the Alberta Congenital Anomalies Surveillance System (ACASS) [50]. The rate of congenital anomalies reported here remains almost double the Canadian national rate for the same birth years (40.3/1000) [160]. There are a number of factors that may increase the risk of congenital anomalies, including suboptimal prenatal nutrition, exposures to alcohol, smoking and other substances and genetic factors [76,161]. Both folate and vitamin A are important in early fetal development and have been identified as nutrients of concern in Arctic regions [76,162,163].

Seventeen percent of women reported taking a multivitamin in the periconceptional period, which is slightly higher than the 13.6% reported for Nunavut women (n=83) from the Canadian Maternity Experiences Survey of 2008 and much lower than the national average of 58% reported by the same survey [31]. Other studies of non-pregnant Inuit women of child bearing years report that 7-11% of Inuit women of child-bearing years take multivitamins [31,129,163]. In a study of 106 Inuit women of child-bearing years residing in Kitikmeot, Schaffer et al.[129] reported that 11% of Inuit women reported taking a multivitamin and 28% had inadequate levels of folate. In a more recent study of 249 non-pregnant Canadian Inuit women of childbearing years from the Inuit Health Survey (2007-2008), Duncan et al.[163] reported that 7% of Inuit women took vitamins containing folic acid and 47% had inadequate folate levels. The low rate of peri-conceptional vitamin use in this and other studies is notable. Peri-conceptional use of

vitamins which include folic acid has been shown to reduce certain congenital anomalies [164,165]. Health promotion strategies may be considered in this area; however, more in-depth study as to attitudes towards vitamin use may be needed to effectively address this issue.

2.4.2 Infant mortality

Indigenous populations worldwide experience infant mortality rates that are substantially higher than national averages [166–168] and Inuit regions of Canada have infant mortality rates at least three times the national average [3,169,170]. Based on results from the current study, the rate of infant mortality remains high for Inuit infants in Nunavut at 19.8/1000 infants, four times the national rate for the same time period (4.9/1,000 live births) [9]. SIDS and SUDI combined continues to be the leading cause of infant death in Nunavut, which is consistent with my previous analysis (1999-2011) [12].

SIDS was the leading cause of infant death in Inuit regions of Canada between 1990 and 2000 (5.2/1,000 live births), and Inuit infants living in Quebec between 1996 and 2010 (4.2/1,000 live births) [3,170]. SIDS has also been reported as the leading cause of infant death in the indigenous populations of Western Australia (4.7/1,000; 1998–2001) [166] and Alaska (3.6/1,000; 2000–2003) [166,167]. Infant death due to infection was also high in the current study (2.4/1,000) and more than seven times the national rate 0.31/1,000 live births (2003-2007) [64], supporting my previous analysis showing 2.1/1000 [12].

Infant deaths due to SIDS and SUDI may be prevented with reduced exposure to prenatal and postnatal tobacco smoke exposure [171,172] and positioning of infants on their backs while

sleeping [173]. The majority of SIDS/SUDI cases in Nunavut between 1999 and 2011 had two or more sleep-related risk factors present including non-supine sleep position and/or bed-sharing with non-caregiver(s) [12]. In an effort to improve maternal child health and reduce infant deaths due to SIDS and SUDI, the Government of Nunavut started the baby box initiative in 2016, which encourages early prenatal care and promotes safe sleep environments and breastfeeding [174].

2.4.3 Maternal and household characteristics

Several indicators associated with adverse early child health outcomes were prevalent in the cohort, including prematurity, food insecurity, household crowding and tobacco smoke exposure. Using data from Nunavut-specific prenatal, labour/delivery and well-baby records allowed collection of population level data for many of these indicators.

Breastfeeding has been shown to reduce risk for child health outcomes like infant mortality, chronic diseases and infectious illness [6,175]. Recent studies have reported that breastfeeding initiation is lower in Nunavut than the national average of 90% [10,29,176]. When all children were included in analysis, 74% of women reported initiating breastfeeding in the current study, which is similar to results from the 2006 Aboriginal Children Survey which reported breastfeeding initiation of 74% for Inuit infants residing with biological parents [71] and higher than results from the Nunavut Inuit Child Health Survey of 68%. However, my results show that breastfeeding initiation was higher in infants not undergoing custom adoption and much closer to the national average at 86%. This finding replicates the results of the 2007-2008 Nunavut Inuit Child Health Survey (n=374 children aged 3-5years) which reported breastfeeding initiation was

85% in a subgroup of caregiver reports from biological mothers [153]. Traditionally, Inuit women breastfed children until three years of age or longer [177]. Health Canada recommends exclusive breastfeeding for at least six months since longer duration of breastfeeding is protective against infectious illness in infancy [178]. In current study, 47% of children not undergoing custom adoption were still being breastfed at 6 months of age and 33% were still being breastfed at 12 months of age.

Prenatal smoking, especially heavy smoking, is associated with a number of adverse birth outcomes, including prematurity, low birth weight, small for gestational age and infant mortality [30,31,179]. Prematurity in itself increases the risk for infant mortality and respiratory infection [180,181]. Although the majority of women in this study reported smoking (84-86%), only 14-17% of women reported heavy smoking (>10 cigs/day), slightly less than the 20% reported for Inuit women residing in Qikiqtaaluk between 2000-2003 [30]. Heavy smoking during pregnancy has been identified as marker for risk factors that influence birth outcomes. In a review of Qikiqtaaluk births between 2000-2003, Mehaffey et al.[30] reported that women who reported heavy smoking during pregnancy (>10 cigs/day) were at significantly higher risk for the adverse birth outcomes. Those results were later duplicated in a much larger study (n=237,470) of adverse birth outcomes in British Columbia [179]. Interestingly, Mehaffey et al.[30] also reported that light smokers (<5 cigarettes per day) had better outcomes than the national average. The authors speculated that light smokers may have stopped smoking after reporting on the first prenatal visit which may explain the better birth outcomes compared to moderate smokers [30]. In current study, 35% of women reported they were either non-smokers or light smokers (<5

cigs/day). Maternal smoking varied between regions and women living in the Kitikmeot region reported lower levels of heavy smoking in both the prenatal and postnatal period.

Country food use was high in the cohort, with up to 80% of children eating country food at least once/week and one in three eating country food daily. In their study of country food use using data from the Inuit Child Health Survey, Johnson-Down and Egeland [182] report that 33% of children were high consumers of country food (>30 times per month). The authors also report that high country food consumers had higher intakes of other important nutrients, including vitamins A and D, iron, magnesium and zinc. However, results from the Nunavut Inuit Children Health Survey also showed high rates of food insecurity [32]. Food insecurity in childhood can significantly impact on health and well-being, including reduced growth and increased risk for infectious illness and nutritional deficiencies like anemia [183–185]. Food insecurity was reported for 42% of children in the current study, which falls between that reported by the Nunavut Inuit Child Health Survey of 56% [32] and the 2006 Aboriginal Children's Survey of 39% [33].

There is a direct association of household crowding with adverse health outcomes including respiratory and other infectious illness [74,186,187]. Statistics Canada reports that 43% of Inuit children live in crowded homes (more than one person per room including bedrooms, living rooms and kitchens) compared to 7% for non-Aboriginal Canadian children [34]. Although the results reported here are not directly comparable, 51% of children lived in homes with more than two people per bedroom, 18% lived in homes with more than three people per bedroom. There

was also a mean of six people living in homes, which replicates results from previous studies [10,46].

2.4.4 Infectious Illness

Hospital admissions of infants for LRTI has been an ongoing area of concern for Nunavut. One in five Inuit infants were hospitalized for LRTI with an admission rate of 295/1,000 Inuit infants, representing a significant burden of infant and child morbidity and significant costs to both families and health care delivery [37,188]. Respiratory syncytial virus (RSV) has been identified as a key contributor to infant admissions for LRTI in Nunavut [6,8,40]. The rate of infant admission associated with RSV reported here (71.8/1,000) is similar to the rate for Nunavut infants born in 2009 reported by Banerji et al.[4] (75.3/1,000 live births). However, only half of infant admissions for LRTI had RSV test results documented, which was even lower in Kivalliq at 30%, so these results should be interpreted with caution.

Otitis media was also prevalent, 86% of children had otitis media at least once, higher than the 50% reported for Canadian children [54] and similar to results from the Nunavut Inuit Health Survey which found 85% of preschoolers had received treatment at least once for an ear infection [10]. Just over half of children experienced three or more episodes of otitis media, which was highest in Kitikmeot. Otitis media is divided into two main types, acute otitis media and otitis media with effusion. Acute otitis media is an infection of the middle ear with acute onset of signs and symptoms caused by middle ear inflammation accompanied by fluid and made up the majority of cases in this study. Otitis media with effusion is the presence of fluid in the middle ear without signs of infection. Fluid in the middle ear causes pressure that prevents the

tympanic membrane from vibrating properly, decreasing sound conduction and hearing [55] Recurrent acute otitis media and otitis media with effusion are associated with impaired hearing at five years of age and can have dramatic impacts on speech development and educational attainment [55–59]. In Nunavut. an estimated 20% of children have some level of hearing loss [189].

Prematurity, tobacco smoke exposure, lack of breastfeeding and crowded housing are all associated with increased risk for infectious illness [6,43,44,46]. In their study of 101 infants from Qikiqtaaluk Nunavut between January 2002 and March 2003, Banerji et al. found admission of children (<2yrs) for LRTI was associated with prenatal smoke exposure (OR:4.0; 95%CI:1.1-14.6), six or more people living at home (OR:2.5, 95%CI:1.1-6.1) and breastfeeding not initiated (OR:3.6, 95%CI:1.2-11.5) [6]. The authors also found that Inuit infants with four Inuit grandparents had increased risk of admission for LRTI than non-Inuit children and suggested that a genetic predisposition may also contribute to the higher rates of infectious illness in Inuit children.

Studies of respiratory tract infections in northern Indigenous populations have identified a genetic variant of the fatty acid oxidation enzyme needed to use fat for energy during fasting that may contribute to adverse child health outcomes. This variant, the p.P479L variant of carnitine palmitoyltransferase 1A, is prevalent in Inuit, Alaska Native and coastal British Columbia First Nations populations and has been associated with increased risk for infectious illness including hospital admission for LRTI and episodes of otitis media in early childhood as well as infant death due to SIDS, SUDI or infection [12,15–18]. Studies are under way to better understand

whether the variant contributes to the high rates of adverse infant and child health outcomes in Inuit children of Nunavut in the broader context of other risk factors, including socioeconomic status.

2.5 LIMITATIONS

This was a retrospective chart review cohort study, all communities with 20 or more births per year were included in the study. Seven communities with a range of 2-20 births/year (accounting for approximately 264 charts during the study period) could not be included due to time, travel, housing and cost constraints. The study collected information for live births to Inuit women residing in Nunavut. Stillbirths and terminated pregnancies were not ascertained, which may impact ascertainment of congenital anomalies. Neonatal deaths that occurred out of territory are likely under-represented especially for neonatal deaths during the first hospitalization (for example extreme prematurity and severe congenital anomalies) and rates reported here may be lower than reported by Statistics Canada which collects this data from all provinces and territories [9]. Data otitis media and gastroenteritis are based on reasons for visit (primary and secondary), testing results and treatments administered (e.g. antibiotics) as entered into the chart. Although this may have led to over-estimation of the prevalence for the outcomes, the proportion of children with otitis media in this study replicates the results found for pre-school aged children in the Nunavut Inuit Health Survey. Maternal and well-baby record data were not available for all records. Information on smoking, vitamin use, food security and household crowded were based on self-reported information and were not available for all records, often due to time limitations when human resources in health centres are limited. Results for these

variables should be interpreted with caution; however, the results reported for many of these variables were similar to previously published data.

2.6 CONCLUSION

Here I present the results of the largest population-based study of birth outcomes and child health for Inuit children living in Nunavut to date, covering just over 80% of births to Inuit women in all regions in Nunavut. Inuit children in Nunavut continue to experience high rates of hospital admission for respiratory tract infection, including RSV, rates that have mostly remained unchanged from previous studies. These high rates represent significant early childhood morbidity and long-term impacts on health and a significant portion of infant mortality. There are many risk factors associated with these outcomes that are well known in Nunavut, including crowded housing and food insecurity, both of which were common in this study. There were also high rates of congenital anomalies, prematurity, infant death and deaths due to SIDS/SUDI. Current efforts promoting safe sleep since the time of the study might be addressing the high rates of SIDS/SUDI. The distribution of outcomes varied by region, suggesting that some outcomes may have a greater contribution to overall child health in those regions. These results provide information on key infant and child health outcomes for health care delivery and health promotion strategies for health care providers, public health representatives, governmental representatives and the local Inuit organization, Nunavut Tunngavik Inc.

CHAPTER 3. NEONATAL HYPOGLYCEMIA AND THE CPT1A p.P479L VARIANT IN TERM NEWBORNS: A RETROSPECTIVE COHORT STUDY OF INUIT NEWBORNS FROM KIVALLIQ NUNAVUT (PAPER 2)

3.1 INTRODUCTION

Neonatal hypoglycemia in the first days of life can largely be prevented by recognizing those at risk and managing them accordingly [190]. Newborns considered at increased risk for neonatal hypoglycemia include those born preterm (<37weeks gestation), small for gestational age (<10th percentile), large for gestational age (>90th percentile), newborns of mothers with diabetes, preeclampsia or hypertension, and newborns with inborn errors of metabolism such as fatty acid oxidation disorders or with higher demands for glucose (sepsis, asphyxia, other perinatal stress) [191–197]. Reported neonatal hypoglycemia incidences vary from 10-14% for healthy term newborns with no risk factors for hypoglycemia (term-NRF, ≥37weeks gestation) [191,198,199] to 18%-66% for at-risk newborns [200–204].

The Canadian Paediatric Society (CPS) defines neonatal hypoglycemia as blood glucose values of ≤2.0mmol/L at 2 hours or <2.6mmol/L from 2 to 48 hours of life and currently recommends screening asymptomatic *at-risk newborns* at 2 hours after their first feed and to continue screening prior to feeds up to 48 hours of life if low values persist (Figure 3.1) [190]. Blood glucose values between 1.8-2.0mmol/L at 2 hours or 2.0-2.5mmol/L after 2 hours are treated with an immediate feed and follow up testing. Intravenous dextrose should be initiated in symptomatic newborns for blood glucose values <1.8mmol/L at 2 hours, ≤2.0mmol/L after 2 hours, or values repeatedly between 2.0-2.6mmol/L.

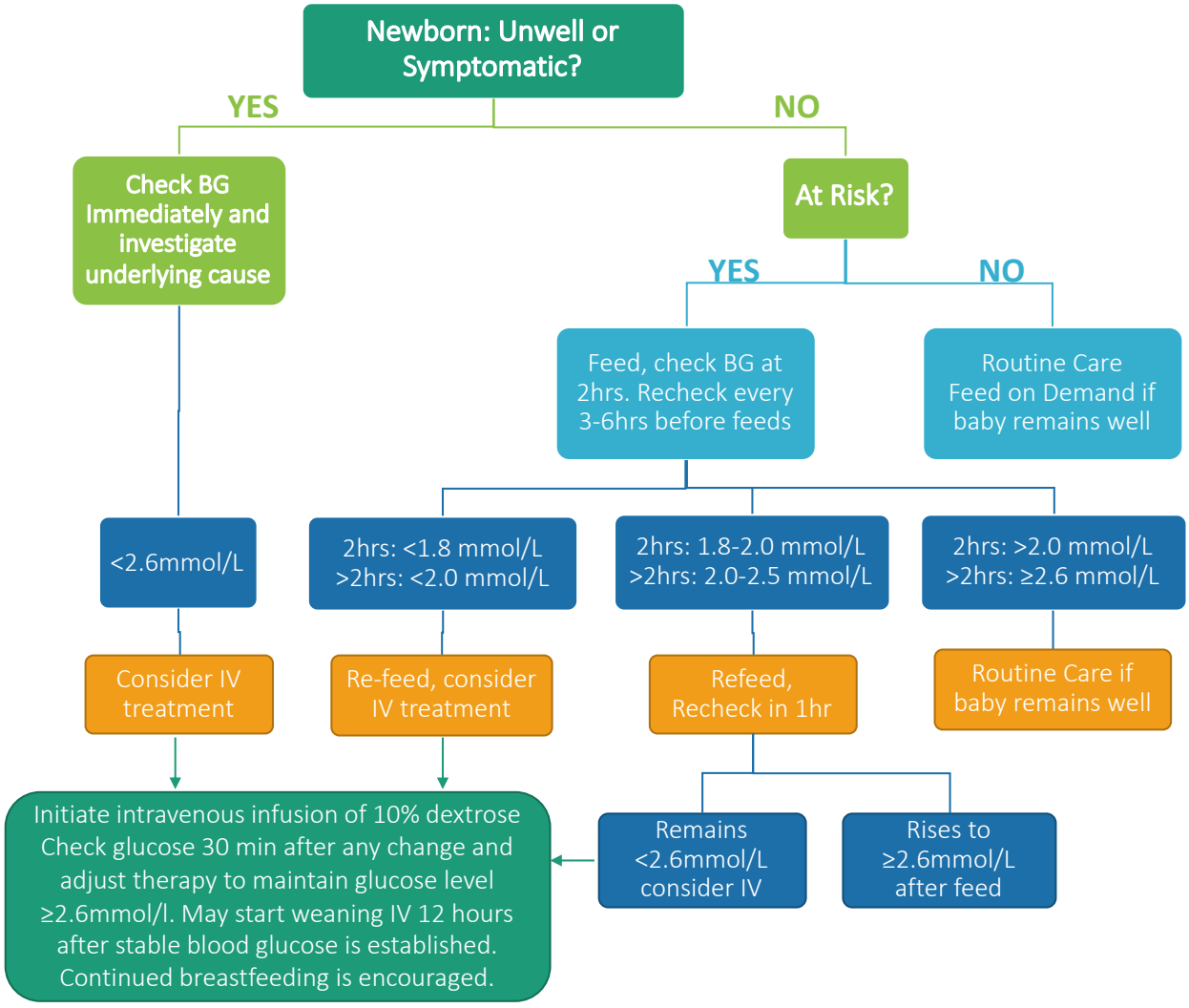

Figure 3.1 Canadian Paediatric Society (CPS) algorithm for the screening and immediate management of babies at risk for neonatal hypoglycemia (2004).
Symptomatic and unwell newborns are screened immediately (jittery, lethargic), 'at risk' newborns that are not symptomatic are screened at 2 hours of life and then every 3-6 hours as needed. Blood glucose values of ≤2.0mmol/L at 2hrs or <2.6mmol/L thereafter are treated with feeding if the newborn is asymptomatic. Newborns with repeated or recurrent low values or values below 1.8 or 2.0mmol/L can also be treated with IV dextrose. At-risk category includes prematurity (<37weeks gestation), small for gestational age (<10th percentile), large for gestational age (>90th percentile), maternal diabetes (pre-existing for gestational), perinatal stress and newborn metabolic disorders (inborn errors of metabolism). Adapted from the CPS screening guidelines for newborns at risk for low blood glucose, 2004 [190].

Classic carnitine palmitoyltransferase 1A (CPT1A) deficiency is a rare autosomal recessive fatty acid oxidation disorder presenting in infancy as hypoketotic hypoglycaemia and metabolic decompensation triggered by fasting or prolonged exercise [108]. CPT1A is an enzyme in the liver and other tissues needed to use long-chain fatty acids for energy during fasting [19].

The CPT1A p.P479L variant (*CPT1A* c.1436C>T, p.P479L, rs80356779) is prevalent in northern Indigenous populations in Canada, Alaska and Greenland [17,20,116–118]. The p.P479L variant is considered a mild variant since it has higher residual activity than other variants causing classic CPT1A deficiency [14,109] . Studies report that infants and children with the p.P479L variant may be at risk for a number of adverse health outcomes, including early childhood hypoglycaemia [13,14], seizures [23], hospital admission for infectious illness [15,18] and unexpected infant death [12,16,17].

The northern Canadian territory Nunavut has high rates of preterm birth (14.0%) and births that are large for gestational age (13.9%) [205]. Nunavut also has a remarkably high prevalence of the CPT1A p.P479L variant (~70% of newborns are homozygous) [20]. Due to concerns that the CPT1A p.P479L variant may increase the risk for neonatal hypoglycemia, all newborns from Kivalliq born in Winnipeg Manitoba are screened for neonatal hypoglycemia. I analyzed blood glucose screening data for Inuit newborns from Kivalliq, born in Winnipeg over a four-year period (01-Jan-2010 to 31-Dec-2013) to determine whether the p.P479L variant is associated with increased risk of neonatal hypoglycemia.

3.2 METHODS

3.2.1 Ethics

Study ethics approval was granted by University of British Columbia and University of Manitoba Research Ethics Boards, and research license from the Nunavut Research Institute. Research was developed and conducted in partnership with Nunavut Tunngavik Inc. and Government of Nunavut Department of Health.

3.2.2 Chart review

Newborn clinical charts were reviewed for Inuit births from 1-Jan-2010 to 31-Dec-2013 (n=728) to mothers residing in the Kivalliq region of Nunavut born at Women's Health Science Centre and St Boniface Hospital, Winnipeg Manitoba. Study inclusion criteria consisted of Inuit newborns with blood glucose measured at least once at 2 to 48 hours of life. Information collected included blood glucose values, maternal and infant characteristics, gestational age, birth weight, perinatal exposures and complications, admission to NICU and interventions. Inuit ethnicity was determined using mother's ancestry indicated on the chart. Newborns were classified as at-risk for neonatal hypoglycemia if any of the following were present: PTB, SGA, LGA, maternal diabetes (pre-existing or gestational), maternal hypertension, maternal preeclampsia, major congenital anomalies, sepsis, asphyxia, or other perinatal stress (resuscitation at birth, transient tachypnea of newborn, chorioamnionitis or major infections). Lowest blood glucose (mmol/L) was calculated using the lowest reading recorded for each newborn on a sample collected at 2 to 48 hours of age and prior to any intravenous dextrose. neonatal hypoglycemia was defined as blood glucose ≤2.0mmol/L at 2 hours of life or <2.6mmol/L from 2 to 48 hours [190], using point-of-care glucometers.

3.2.3 Genotype analysis

CPT1A p.P479L (rs80356779) genotyping was conducted by the newborn screening program at Cadham Laboratory in Winnipeg Manitoba for all infants born to mothers residing in Kivalliq. Genotyping for the p.P479L variant in the *CPT1A* gene was performed as follows: A 3mm disc was punched from each neonatal whole blood specimen collected on filter paper, fixed in absolute methanol and evaporated to dryness and used directly as the sample source in an allele-specific PCR amplification with the following reagents: 20mM Tris–HCl, 50 mM KCL, pH 8.4, 2 mM MgCl2, 0.4 μM *CPT1A* primers, 0.15 μM b-globin primers and 2.5 U platinum Taq polymerase. Genotyping was performed in parallel duplicate tubes of each specimen and were amplified by an allele-specific PCR mutation strategy (AS-PCR) each containing a common forward primer and a mutant or wildtype reverse primer for the p.P479L variant, producing an 187bp product. A 187bp *CPT1A* fragment was amplified using a common forward primer and either a mutant 5' CCAAAGGTGGGCCACGATGA 3' or wildtype 5' CCAAAGG TGGGCCACGATGG 3' reverse primer differing by a single base mismatch at the 3' end. Nucleotide A is complementary to T at position 1436 in the variant allele of mutant reverse primer and nucleotide G complementary to C at position 1436 in the variant allele of mutant reverse primer. A mismatch G was added at the penultimate base in both reverse primers to increase specificity of the PCR reaction. Products were visualized by gel electrophoresis with the wildtype reverse primer when the wildtype allele was present, and mutant reverse primer when the mutant allele was present. Primers amplifying a 268bp segment of the β-globin gene were included in each reaction tube to verify specimen integrity and the absence of inhibitors. Genotype results were linked to chart data using infant and maternal data and was successful for 92.4% (569/616) of charts.

3.2.4 Statistical analysis

I conducted univariable tests of statistical significance using linear and logistic regression to explore relationships between variables and outcomes (mean lowest blood glucose and neonatal hypoglycemia). I used pairwise correlation tests to show the inter-relationships between the variables. Crude odds ratios with 95% confidence intervals were considered statistically significant for two-tailed p-values<0.05. The multivariable logistic regression model included biological risk factors for neonatal hypoglycemia and any variables with p values <0.10 in univariable analysis. The model for all newborns included gestational age, size for gestational age, maternal diabetes, maternal hypertension, maternal preeclampsia, other clinical risks for hypoglycemia, birth year, sex and *CPT1A* genotype. The term-NRF newborn model included gestational age, birth year, sex and *CPT1A* genotype. Due to collinearity with gestational age, birth weight was excluded from models. Hardy-Weinberg equilibrium (HWE) was analyzed using the $\chi 2$ test with $p<0.05$ significance level. Analysis was preformed using Stata11 IC [206]. STROBE cohort reporting guidelines were used.

3.3 RESULTS

Charts for 728 Inuit infants were reviewed. Records missing blood glucose data (n=25) and/or gestational age (n=6) were excluded. An additional 88 records were excluded due to no blood glucose testing at or after 2 hours of life (n=41) or initiation of intravenous dextrose treatment prior 2 hours or first blood glucose test (n=47). Of the latter category, 72% (63/88) were at-risk newborns. The final cohort was 616 births. Of those, 13.7% were preterm, 6.8% were SGA and 11.2% were LGA. Maternal diabetes (pre-existing or gestational) was reported in 2.6% of births and maternal hypertension without preeclampsia 5.5% (Table 3.1). *CPT1A* p.P479L status was

available for 92.4% (569/616) of those records, 68.7% were p.P479L homozygous, 26.0% were p.P479L heterozygous and 5.3% were non-carriers (Table 3.1). The distribution of p.P479L variant departed from HWE in the study population with an excess of the expected number of homozygous carriers (p=0.003). In pairwise correlation, p.P479L homozygosity was negatively correlated with gestational age, birth weight and large for gestational age; however, there was no correlation to prematurity (Table A.2.1, Sub-Appendix A.2). There was no correlation between birth year and gestational age, but birth in 2010 positively correlated with maternal hypertension and birth in 2011 was positively correlated birth weight.

3.3.1 Incidence of neonatal hypoglycemia

Mean lowest blood glucose did not differ between at-risk and term-NRF newborns at 2.9mmol/L (Table 3.1). However, mean lowest blood glucose was significantly lower for newborns of mothers with hypertension (2.6mmol/L, 95%CI:2.4-2.7, p=0.001) and 2010 births compared to births in 2013 (2.7mmol/L, 95% CI:2.6-2.8, p<0.001). Overall neonatal hypoglycemia incidence was 21.4%. neonatal hypoglycemia incidence in at-risk newborns was 24.4%, varying from 15.1% (LGA) to 52.9% (maternal hypertension, Figure 3.2).

After adjustment for gestational age, size for gestational age and sex, the adjusted ORs for hypoglycemia were 3.33 for maternal diabetes (95%CI:1.04-10.68, p=0.04), 3.36 for maternal hypertension without preeclampsia (95%CI:1.53-7.40, p=0.003), 1.72 for male infant (95%CI:1.12-2.62, p=0.01) and 2.33 for 2010 births (95%CI:1.23-4.41, p=0.01). The adjusted ORs were 2.14 for *CPT1A* p.P479L homozygotes (95%CI:0.69-6.60, p=0.19) and 1.87 for p.P479L heterozygotes (95%CI:0.58-6.03, p=0.30), compared to non-carriers (n=30).

Table 3.1 Neonatal hypoglycemia (2 to 48 hours of life) in Inuit infants born in Winnipeg to mothers residing in the Kivalliq region of Nunavut from Jan 1, 2010 to Dec 31, 2013 (n=616)

		Mean lowest blood glucose (mmol/L)		Neonatal Hypoglycemia			Multivariable Model (n=569)[a]
Variable	**n / mean (%)**	**mean (95%CI)**	**p**	**n**	**% (95%CI)**	**cOR (95%CI)**	**adjOR (95% CI)**
Cohort		2.9 (2.9-3.0)	-	132	21.4 (18.3-24.9)		
Mat. Diabetes							
Yes	16 (2.6)	2.8 (2.4-3.1)	0.41	7	43.8 (19.8-70.1)	2.96 (1.08-8.09)	3.33 (1.04-10.68)
No	600 (97.4)	2.9 (2.9-3.0)	ref		20.8 (17.6-24.1)	ref	
Mat. Htn							
Yes	34 (5.5)	2.6 (2.4-2.7)	0.001	18	52.9 (35.1-70.2)	4.62 (2.28-9.34)	3.36 (1.53-7.40)
No	582 (94.5)	2.9 (2.9-3.0)	ref		19.6 (16.4-22.8)	ref	
Preeclampsia							
Yes	20 (3.2)	3.0 (2.7-3.2)	0.76	5	25.0 (8.7-49.1)	1.23 (0.44-3.45)	1.49 (0.50-4.46)
No	596 (96.8)	3.0 (2.7-3.2)	ref		21.3 (18.0-24.6)	ref	
Clinical Risks							
Yes	61 (9.0)	3.0 (2.8-3.3)	0.06	10	16.4 (8.2-28.1)	0.70 (0.34-1.41)	0.60 (0.29-1.26)
No	555 (91.0)	3.1 (2.8-3.3)	ref		22.0 (18.5-25.4)	ref	
Birth Year							
2010	136 (22.1)	2.7 (2.6-2.8)	0.001	45	33.1 (25.3-41.7)	2.26 (1.27-4.01)	2.33 (1.23-4.41)
2011	171 (27.8)	3.0 (2.9-3.1)	0.23	31	18.1 (12.7-24.7)	1.01 (0.56-1.84)	1.18 (0.62-2.25)
2012	181 (29.4)	2.9 (2.8-3.0)	0.87	33	18.2 (12.9-24.6)	1.02 (0.57-1.83)	1.14 (0.60-2.14)
2013	128 (20.8)	2.9 (2.8-3.0)	ref	23	18.0 (11.7-25.7)	ref	ref
Sex							
Male	313 (50.8)	2.9 (2.8-2.9)	0.18	78	24.9 (20.2-30.1)	1.53 (1.04-2.26)	1.72 (1.12-2.62)
Female	303 (49.2)	2.9 (2.9-3.0)	ref		17.8 (13.5-22.2)	ref	
Birth Weight	3357g					1.00 (0.999-1.00)	
Gestational Age	38.4wks					0.92 (0.81-1.05)	0.91 (0.79-1.05)
PTB (<37wks)	58 (9.4)	2.8 (2.6-3.0)	0.10	15	25.9 (15.3-39.0)	1.31 (0.71-2.45)	
Term (≥37wks)	558 (90.6)	2.9 (2.9-3.0)	ref	117	21.0 (17.6-24.4)	ref	
Size for GA							
Ave (10-90th)	506 (82.1)	2.9 (2.8-2.9)	ref	112	22.2 (18.6-26.0)	ref	ref
Small (<10th)	37 (6.0)	2.9 (2.7-3.2)	0.85	9	24.3 (11.8-41.2)	1.13 (0.52-2.46)	1.04 (0.44-2.44)
Large (>90th)	73 (11.9)	3.0 (2.8-3.2)	0.19	11	15.1 (7.8-25.4)	0.62 (0.32-1.22)	0.70 (0.33-1.43)
CPT1A p.P479L	569						
Homozygous	391 (68.7)	2.9 (2.8-3.0)	0.01	89	22.8 (18.7-27.2)	1.92 (0.65-5.63)	2.14 (0.69-6.60)
Heterozygous	148 (26.0)	2.9 (2.8-3.0)	0.01	30	20.3 (14.1-27.7)	1.65 (0.54-5.10)	1.87 (0.58-6.03)
Non-carrier	30 (5.3)	3.2 (2.9-3.5)	ref	4	13.3 (3.8-30.7)	ref	ref
Risk Category							
Term-NRF	374 (60.7)	2.9 (2.9-3.0)	ref	73	19.5 (15.6-23.9)	ref	
At-risk	242 (39.3)	2.9 (2.8-3.0)	0.54	59	24.4 (19.1-30.3)	1.33 (0.90-1.96)	

[a]Multiple logistic regression model included gestational age, size for gestational age, maternal pre-existing or gestational diabetes, maternal hypertension, maternal preeclampsia, other clinical risks for hypoglycemia, birth year, sex and *CPT1A* genotype. Due to collinearity with gestational age, birth weight was excluded from multiple logistic model . Mat DM: maternal diabetes, pre-

existing or gestational. Mat hypertension without preeclampsia. Clinical risks: asphyxia, infection, transient tachypnea of the newborn (TTN), chorioamnionitis and major congenital anomalies. PTB: Preterm birth (<37 weeks gestation). Term-NRF newborns: term newborns (≥37weeks gestation) with no risk factors for neonatal hypoglycemia; excludes preterm birth, small for gestational age, large for gestational age, macrosomia, maternal pre-existing or gestational diabetes, maternal hypertension, maternal preeclampsia, other clinical risks for hypoglycemia. 95%CI: 95% confidence interval.

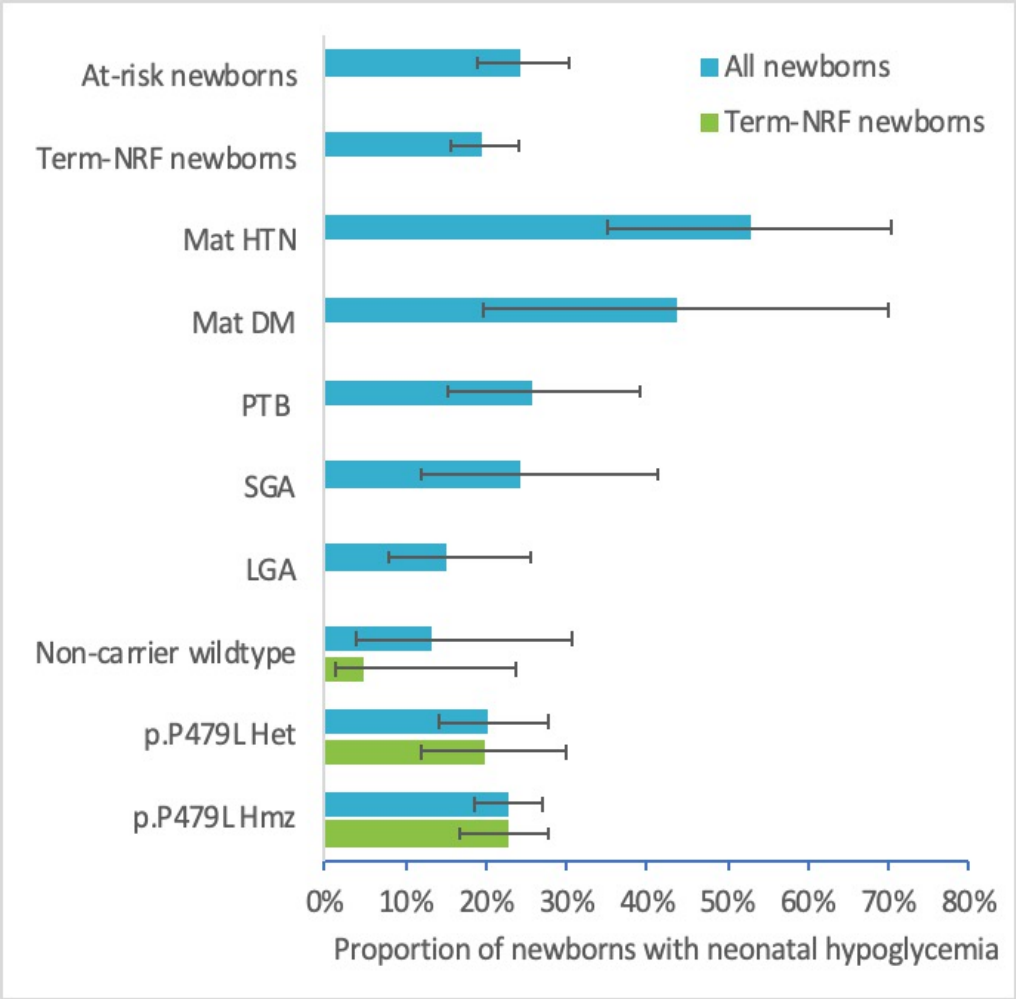

Figure 3.2 Neonatal hypoglycemia in Inuit newborns from Kivalliq Nunavut, 2010-2013
Proportion of newborns with neonatal hypoglycemia by risk group, for all newborns and for term with no risk factors for hypoglycemia (term-NRF) newborns (n=616). Mat HTN: maternal hypertension without preeclampsia. Term-NRF newborns: term newborns (≥37weeks gestation) with no risk factors for neonatal hypoglycemia; excludes preterm birth, small for gestational age, large for gestational age, macrosomia, maternal pre-existing or gestational diabetes, maternal hypertension, maternal preeclampsia, other clinical risks for hypoglycemia. Error bars represent 95% confidence interval

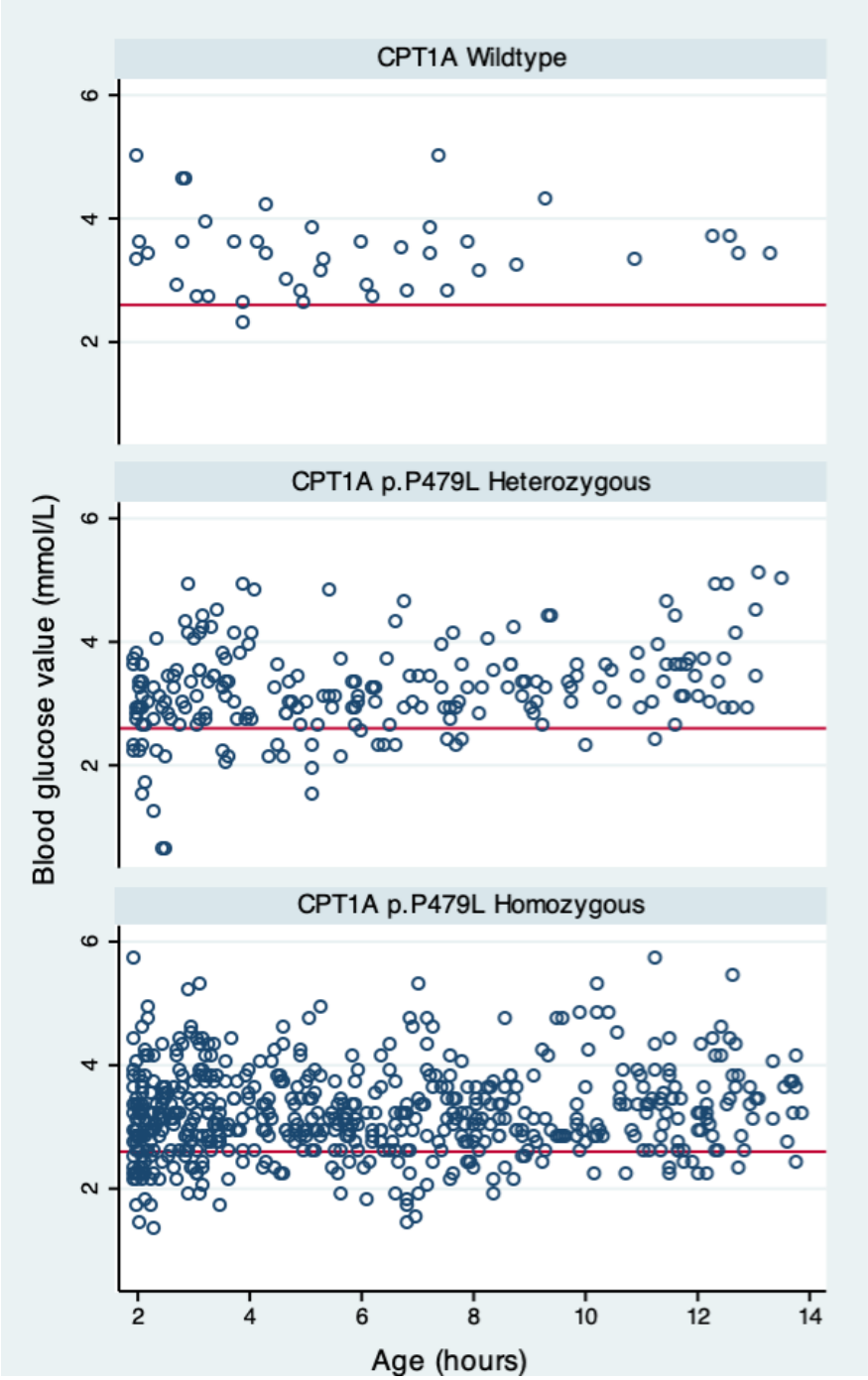

Figure 3.3 Blood glucose values from 2-14hrs of life by *CPT1A* genotype for Inuit infants born term with no risk factors to mothers residing in Kivalliq Nunavut
For newborns born between 2010 and 2013 (n=374). Red reference line at 2.6mmol/L.

Table 3.2 Neonatal hypoglycemia (2 to 48 hours of life) in term Inuit newborns with no other known risk factors (term-NRF) born in Winnipeg to mothers residing in the Kivalliq region of Nunavut Jan 1, 2010 to Dec 31, 2013 (n=374)

Variable	Mean lowest blood glucose (mmol/L)			Neonatal Hypoglycemia				Multivariable Log Model (n=339)[a]	
	n	Mean (95% CI)	p	n	% (95% CI)	cOR (95%CI)	p	adjOR (95% CI)	p
Term-NRF Newborns	374	2.9 (2.9-3.0)		73	19.5 (15.6-23.9)				
Birth Year									
2010	80	2.7 (2.6-2.9)	0.10	19	23.8 (14.9-35.6)	1.15 (0.54-2.44)	0.72	1.38 (0.61-3.12)	0.44
2011	102	3.1 (3.0-3.2)	0.03	17	16.6 (10.0-25.3)	0.74 (0.35-1.58)	0.43	0.93 (0.42-2.07)	0.86
2012	117	2.9 (2.8-3.0)	0.79	21	17.9 (11.5-26.1)	0.81 (0.39-1.67	0.56	0.99 (0.46-2.13)	0.97
2013	75	2.9 (2.8-3.0)	ref	16	21.3 (12.7-32.3)	ref		ref	
CPT1A p.P479L status	339								
Non-carrier	21	3.2 (3.0-3.5)	ref	1	4.8 (0.12-23.8)	ref			
Heterozygous	86	2.9 (2.8-3.0)	0.02	17	19.8 (12.0-29.8)	4.93 (0.62-39.34)	0.13	4.71 (0.59-37.89)	0.15
Homozygous	232	2.9 (2.8-3.0)	0.01	51	22.9 (16.8-27.9)	5.64 (0.74-43.01)	0.10	4.97 (0.65-38.35)	0.12
Sex									
Female	185	3.0 (2.9-3.1)	ref	32	17.3 (12.1-23.5)	ref		ref	
Male	189	2.9 (2.8-3.0)	0.07	41	21.7 (16.0-28.3)	1.32 (0.79-2.22)	0.28	1.41 (0.82-2.42)	0.22
Birth Weight	374					0.999 (0.999-1.00)	0.12		
Gestational Age	374					0.83 (0.66-1.05)	0.13	0.82 (0.64-1.04)	0.10

[a]Multiple logistic regression model included gestational age, birth year, sex and *CPT1A* genotype. Due to collinearity with gestational age, birth weight was excluded from the model. Term-NRF newborns: term newborns (≥37weeks gestation) with no risk factors for neonatal hypoglycemia; excludes preterm birth, small for gestational age, large for gestational age, macrosomia, maternal pre-existing or gestational diabetes, maternal hypertension, maternal preeclampsia, other clinical risks for hypoglycemia. 95%CI: 95% confidence interval.

3.3.2 Neonatal hypoglycemia in term newborns without risk factors

In term-NRF newborns (n=374), mean lowest blood glucose was significantly lower for p.P479L homozygotes (2.9mmol/L, 95%CI:2.8-3.0, p=0.01) and p.P479L heterozygotes (2.9mmol/L, 95%CI:2.8-3.0, p=0.02) compared to non-carriers (3.2mmol/L, 95%CI:3.0-3.5; Table 3.2). Although not statistically significant, a greater number of newborns with the p.P479L variant had blood glucose levels below 2.6mmol/L in the first 14 hours of life (Figure 3.3).

Neonatal hypoglycemia incidence in term-NRF newborns was 19.5% overall, 22.0% for *CPT1A* p.P479L homozygotes, 19.8% for p.P479L heterozygotes and 4.8% for non-carriers (Table 3.2). After adjustment for gestational age, sex and birth year in term-NRF newborns, the adjusted OR was 4.97 for *CPT1A* p.P479L homozygotes (95%CI:0.65-38.35, p=0.12) and 4.71 for p.P479L heterozygotes (95%CI:0.59-37.89, p=0.15), compared to non-carriers (n=21).

3.4 DISCUSSION

Neonatal hypoglycemia incidence in Inuit infants from the Kivalliq region of Nunavut was 21.4%. NH incidence in at-risk newborns (PTB, SGA, LGA, macrosomia, maternal diabetes, maternal hypertension, maternal preeclampsia, other clinical risks) was 24.4%, within the expected range of other published results studies (17.9%-65.5%, Table 3.3) [200–204].

The incidence of neonatal hypoglycemia was high in newborns of mothers with hypertension (52.9%). Pregnancy-induced hypertension (PIH) increases risk for intrauterine growth restriction and subsequent neonatal hypoglycemia [207]. As well, beta-blockers used to control PIH may increase risk of neonatal hypoglycemia. Although two smaller studies did not find an association

between beta-blocker use and neonatal hypoglycemia [207,208], a larger study found a higher incidence of neonatal hypoglycemia in those exposed to beta-blockers in late pregnancy (4.3% versus 1.2%) [209]. The American Pediatric Endocrine Society [197] includes both maternal hypertension and preeclampsia as risk factors for neonatal hypoglycemia in their screening guidelines. At the time of the study, the CPS screening guidelines did not include maternal hypertension as a risk factor for neonatal hypoglycemia [190]; however, a recent update of the guidelines in 2019 includes maternal use of the beta-blocker labetalol as a risk factor for neonatal hypoglycemia [210].

When only those infants without typical risks for neonatal hypoglycemia were considered (term-NRF newborns), the incidence of neonatal hypoglycemia was 19.5%. While the majority of studies on neonatal hypoglycemia focus on at-risk newborns; there are a number of studies on term-NRF newborns; which report neonatal hypoglycemia incidences of 10-14% (Table 3.3) [191,198,199]. However, these studies used protocols that differ from current CPS screening guidelines, making direct comparisons with this study challenging. Further study is indicated to clarify the expected incidence of neonatal hypoglycemia in term-NRF newborns using current screening criteria and current methods of testing.

Table 3.3 Comparison of reported incidences of neonatal hypoglycemia in published literature.

Article	Sample size	Neonatal Hypoglycemia			Severe Hypoglycemia			Blood Glucose Tests		Inclusion Criteria	Exclusion Criteria	Population
		Defn	num	%	Defn	num	%	Timing	Mean #			
At Risk Newborns:												
Lucas et al. 1988 [200]	661	<2.6	433	65.5%	-			0-24hrs	3	BW<1850g		Multicentre, UK
Harris et al. 2012 [201]	514	<2.6	260	51.0%	≤2.0	97	19.0%	0-48hrs	6	Late PTB (35-36wks)	Early PTB (<35wks)	
Hosagasi et al. 2018 [202]	207	≤2.2 0-4hrs / <2.6 4-24hrs	37	17.9%	<1.5 0-4hrs / <2.0 4-24hrs	11	5.3%	0-24hrs	8	SGA, LGA, PTB, Macrosomia, IDM	Term, CAs, Perinatal risks (Prenatal & Clinical risks)	Ankara, Turkey
James-Todd et al. 2018 [203]	515	<2.2	213	41.4%	-			0-48hrs	3	Early PTB (<32wks)	Term, IDM	Boston, USA
Blank et al. 2018 [204]	1570	<2.2	762	48.5%	<1.5	271	17.3%	0-24hrs	5	Mod PTB (34-36wks)	Early PTB (<34wks), Clinical risks	Nijmegen, Netherlands
Current study	242	<2.6	59	24.4%				2-48hrs	3	PTB, SGA, LGA, IDM, Clinical risk, p.P479L hmz, het or non-carrier, Mat. HTN, Preeclampsia	Term	Kivalliq Inuit infants born in Winnipeg
Term At Risk Newborns												
Heck and Erenberg 1986 [192]	114	<2.2	33	28.9%	<1.8	9	7.9%	0-52hrs	6	Term, SGA, LGA	PTB, Clinical risks, Mat HTN	Iowa USA
Hawdon et al 1992 [193]	156	<2.6	19	12.0%	-			0-6 days	1	Term, LGA, Prenatal risks	PTB, SGA, IDM	Newcastle upon Tyne, UK
Cole and Peevy 1994 [211]	60	<2.2	N/A	40.0%	-			0-2hrs	1	Term, AGA, Perinatal risks (Prenatal & Clinical risks)	SGA, LGA	USA
Johnson 2003 [212]	157	<2.2	20	12.7%	-			2hrs	1	Term, LGA, SGA	PTB, LBW, IDM, Clinical risks	USA

Article	Sample size	Neonatal Hypoglycemia			Severe Hypoglycemia			Blood Glucose Tests		Inclusion Criteria	Exclusion Criteria	Population
		Defn	num	%	Defn	num	%	Timing	Mean #			
Term-NRF Newborns												
Lubchenco and Bard 1971 [191]	126	-			<1.7	12	10.0%	0-4 days	3	Term (38-42wks)	PTB (<38wks), >42wks, SGA, LGA	Colorado, USA
Srinivasan et al. 1986 [198]	60	-			<2.0	8	13.3%	0-3hrs	3	Term	PTB, SGA, LGA, IDM, LBW, Macrosomia(>4000g), Clinical risk	Chicago, USA
Hoseth et al. 2000 [199]	223	<2.6	31	14.0%	<1.8	1	0.4%	1-96 hrs	1	Term	PTB, SGA, LGA, IDM, clinical risks, Apgar1min>7, 5min=10	Denmark
Current study	374	<2.6	73	19.5%				2-48hrs	3	Term, *CPT1A* p.P479L hmz, het or non-carrier	PTB, SGA, LGA, IDM, Clinical risks, Mat HTN, Preeclampsia	Kivalliq Inuit infants born in Winnipeg

N/A: Not available. PTB: preterm birth; SGA: small for gestational age; LGA: Large for gestational age; IDM: infant of a diabetic mother, Mat HTN: Maternal hypertension

CPT1A p.P479L homozygous and heterozygous term-NRF newborns had significantly lower values of mean lowest blood glucose compared to term-NRF newborns without the variant (2.9 versus 3.3mmol/L), although the mean value was above the clinical neonatal hypoglycemia threshold of 2.6mmol/L. Term-NRF newborns with the *CPT1A* p.P479L variant (homozygous and heterozygous) also had higher incidences for neonatal hypoglycemia compared to non-carrier term-NRF newborns. Unfortunately, there was insufficient sample size to detect a statistically significant difference within the clinically meaningful differences between genotypes. It is important to note that the majority of *CPT1A* p.P479L homozygotes and heterozygotes with neonatal hypoglycemia had blood glucose values between 2.0-2.6mmol/L, which is usually treated with an immediate feed unless the newborn is symptomatic or has repeated or prolonged neonatal hypoglycemia.

CPT1A p.P479L homozygotes and heterozygotes had similar neonatal hypoglycemia incidences, representing a possible heterozygous effect, which is interesting since classic CPT1A deficiency is considered an autosomal recessive disorder. This could represent impaired ketogenesis and glucagon secretion for both homozygote and heterozygote neonates. Interestingly, a potential heterozygote effect is also reported by Sinclair et al.[18], although outcomes in that study were for hospital admissions with infection (presumably impaired immune system function). Term-NRF newborns without the variant (non-carriers) had a lower incidence of neonatal hypoglycemia than the expected 10-14% published for term-NRF newborns [191,198,199]; however, given the very low numbers of non-carrier term-NRF newborns in the study, further research is needed to determine if this accurately represents neonatal hypoglycemia incidence in Inuit term-NRF newborns without the variant.

At birth, blood glucose levels in newborns naturally fall to a nadir at 1 to 2 hours of life and then begin to rebound at 2 to 3 hours with a mean blood glucose of 3.1-3.3mmol/L in the first 48 hours [191,193,194], rising to normal by 72 hours of life as newborns adapt to intermittent feedings [192,198,199]. This transient neonatal drop in glucose concentration occurs in all mammals and may be important in stimulating a number of physiological pathways needed in postnatal life, including adapting to fast-feed cycles and stimulating appetite [213].

Newborns with the CPT1A p.P479L variant may be more likely to develop neonatal hypoglycemia in the first days of life due to the critical role CPT1A plays in energy homeostasis. Both ketone production in the liver (ketogenesis) and glucagon secretion from the pancreas are dependent on CPT1A activity [79,84]. At birth, glucagon levels dramatically rise, stimulating glycogen breakdown, glucose production, hepatic *CPT1A* expression and ketogenesis [82,102,196,199]; ketogenesis is blunted for the first 24hrs, but rises at 24-72hrs of life relative to low glucose concentration [193,196]. Since glucagon secretion is dependent on CPT1A activity [82], stimulation of glycogen breakdown, glucose production and hepatic *CPT1A* expression may be inadequate in newborns with the CPT1A p.P479L variant, which could impair their ability to adapt to postnatal fast-feed cycles.

The distribution of the p.P479L variant deviated from HWE in this study, which was limited to Kivalliq Inuit births in Winnipeg. A number of Kivalliq births occur outside Winnipeg each year (~30), which may affect HWE calculations given a previous population evaluation reported HWE for this allele [20].

Neonatal hypoglycemia incidence was significantly higher for 2010 births in the overall cohort, but not for 2010 births in the term-NRF newborn subgroup. Prior to 2011, the CPS recommended testing prior to first feed at 1 to 2 hours of life. In 2011, the recommendation changed to initiate testing at 2 hours after the first feed. The change in neonatal hypoglycemia screening protocols in 2011 likely explains the observed rate of neonatal hypoglycemia in 2010 newborns when testing was conducted prior to the first feed, when blood glucose levels are lowest in neonates [191,193,194].

A number of studies report long-term neurological effects for severe, prolonged, recurrent or symptomatic neonatal hypoglycemia in at-risk newborns [200,214,215]. There are questions regarding the current thresholds for intervention in asymptomatic neonatal hypoglycemia [216–218], given the potential impact on clinical resources and possible iatrogenic adverse effects [196,219,220]. A recent meta-analysis by Shah et al.[221] determined that only one study demonstrated strong evidence of long term developmental outcomes for neonatal hypoglycemia in at-risk newborns. This study, by McKinley et al.[215], reported a 2-3 fold increased risk of impaired executive function and visual motor performance at 4.5yrs in children who were at-risk newborns (PTB, SGA, LGA, maternal diabetes) with documented neonatal hypoglycemia (<2.6mmol/L) in the first 1-7days of life, indicating that current thresholds recommended for management are clinically relevant for at-risk newborns. However, there have not been similar studies in term-NRF newborns, so it is unclear whether asymptomatic neonatal hypoglycemia in term-NRF newborns represents a similar risk of long-term neurological effects.

Food insecurity are is prevalent in Nunavut [32] and changes to the Government of Canada food subsidy the Nunavut to a market-driven food retail subsidy program in 2011 may have actually increased food insecurity in the territory [49], which may have implications with neonatal hypoglycemia. It was not possible to assess the impact of food security in the current study and further exploration of this issue is warranted.

3.5 LIMITATIONS

This was a retrospective chart review study. Although it was routine to screen all Inuit infants for neonatal hypoglycemia in the cohort, testing times, frequency and documentation of tests varied. In this study, only 5% of newborns did not have the CPT1A p.P479L variant, which likely precluded identifying statistical significance for neonatal hypoglycemia in those with the variant. p.P479L homozygosity was negatively correlated with gestational age, but not prematurity, although that may be due to small sample size. Approximately 30 births/year occur within Kivalliq or at other secondary hospitals serving the region and are not included in this study. The CPT1A p.P479L variant was the only variant studied. The analysis was limited to Inuit children; however, non-Inuit admixture could not be assessed in the study.

3.6 CONCLUSION

The incidence of neonatal hypoglycemia was high in term Inuit infants without typical risk factors for hypoglycemia born in Winnipeg, Manitoba to mothers from Kivalliq. My results show that otherwise well newborns from this region with the p.P479L variant (either homozygous or heterozygous) have an incidence of neonatal hypoglycemia which was similar to newborns with established risk factors. However, the number of newborns without the variant in this study was

very small, possibly due to historical selective advantage of the variant, affecting statistical significance in the study.

To date, outcome research on neonatal hypoglycemia has focused on at-risk newborns, which may be confounded by other risk factors for adverse long-term outcomes. Prospective longitudinal studies to determine long-term effect of neonatal hypoglycemia on healthy term newborns in this population may help answer these questions. Current guidelines suggest blood glucose screening for at-risk newborns as standard practice. Multidisciplinary local input is indicated to determine if routine neonatal glucose screening and/or other management is indicated for Inuit infants.

CHAPTER 4. ASSOCIATION OF THE CARNITINE PALMITOYLTRANSFERASE 1A (*CPT1A*) p.P479L ARCTIC GENE VARIANT WITH INFECTIOUS ILLNESS IN EARLY CHILDHOOD (PAPER 3)

4.1 INTRODUCTION

The Canadian territory of Nunavut has high rates of infectious illness, including otitis media in early childhood and infant hospital admissions for lower respiratory tract infection (LRTI; 234-306/1,000) and has an infant mortality rate four times the Canadian average (21.5 vs 4.5/1,000 live births) [4,6,9,10]. Nunavut also has a high prevalence of the carnitine palmitoyltransferase 1A (*CPT1A*) p.P479L gene variant (c.1436C>T, rs80356779) [20], which is common in northern Indigenous populations of Alaska, Canada and Greenland [17,20,118,22,117]. The variant has been associated with a number of adverse early child health outcomes, including neonatal and childhood hypoglycaemia [13,14], seizures [23], hospital admission for infection in early childhood [15,18] and sudden unexpected infant death and infant death due to infection [12,16,17].

CPT1A is a fatty acid oxidation enzyme expressed in the liver and other tissues and is required to use long-chain fatty acids for energy during fasting or prolonged exercise [19]. Classic CPT1A deficiency is a rare autosomal recessive disorder (1:500,000 to 1:1,000,000) presenting during infancy as hypoketotic hypoglycaemia and metabolic decompensation triggered by prolonged fasting and/or vomiting, often precipitated by active infection [108]. The CPT1A p.P479L variant, also known as the ‘arctic variant’, has partial residual activity (2-22% of normal) and is considered a mild variant of CPT1A [14,109]. In Nunavut, ~70% of infants are p.P479L homozygous, and the

variant may have conferred positive health outcomes historically compared to non-carriers [119], possibly due to synergy with traditional diet practices [14,118].

I analysed the infant and child health outcomes of a four-year cohort of 2225 Inuit children residing in Nunavut to determine the prevalence of the variant in Inuit births by Nunavut region and to determine whether the CPT1A p.P479L variant is associated with infectious illness after adjusting for perinatal, postnatal and socioeconomic variables.

4.2 METHODS

4.2.1 Research ethics

Study ethics approval was granted by the University of British Columbia, University of Victoria and University of Manitoba Research Ethics Boards, and a research licence was granted by the Nunavut Research Institute. The study was developed and conducted in partnership with the Government of Nunavut Department of Health, Nunavut Tunngavik Inc. (NTI) and the Qaujigiartiit Health Research Centre (QHRC). NTI is responsible for ensuring the implementation of and adherence to the Nunavut Land Claims Agreement and advocates for policies and programs that enhance Inuit well-being, which includes healthy children. The QHRC is a community-led research institute that fosters local leadership and engagement in research activities involving the health and well-being of Nunavummiut.

4.2.2 Data sources

Clinic charts of Inuit children born from 01-Jan-2010 to 31-Dec-2013 were reviewed in 18 Nunavut communities, including all communities with >20 births/year. Information collected included birth data (e.g. gestational age, birth weight, place and type of birth, complications) perinatal and postnatal exposures from prenatal, labour/delivery, newborn and well-baby records and medical information up to five years of age, including health centre visits, major medical diagnoses, hospital admissions and treatments. Inuit ethnicity was determined using mother's and/or infant's ancestry indicated on the chart. Food insecurity was defined as described in Chapter 2.

Community SES was defined using the 2011 Statistics Canada community well-being (CWB) index. This index is comprised of four components (education, labour force activity, income and housing) calculated from the 2011 National Household Survey and provides a measure socioeconomic well-being for individual communities across Canada [222]. The CWB combines the four components into an index between 0 (lowest) and 100 (highest; Figure A.3.1, Sub-Appendix A3).

Outcome variables were admission for LRTI (>24hrs to regional or tertiary hospital), admission with respiratory syncytial virus (RSV; >24hrs to regional or tertiary hospital for laboratory confirmed RSV), otitis media, gastroenteritis (vomiting and/or diarrhea not otherwise explained) and dental interventions (restorations, extractions, treatment of infection, surgery). Repeat visits/admissions within 14 days were not counted in rates.

4.2.3 Genotyping analysis

CPT1A p.P479L (rs80356779) genotyping was conducted by the newborn screening programme at Cadham Provincial Laboratory in Winnipeg Manitoba for all Kivalliq region newborns, as previously described in Chapter 2. Genotyping for the p.P479L variant in the *CPT1A* gene for infants born in Kitikmeot and Qikiqtaaluk was conducted at the Newborn Screening Ontario at the Children's Hospital of Eastern Ontario and was performed as follows: a 3mm dried blood spot (DBS). Each DBS was fixed with 50 μL of methanol and evaporated under nitrogen. 50 μL of 1X Platinum Tfi reaction buffer (Luminex) was added to each methanol-fixed DBS then heated at 98ºC for 40 minutes and frozen. The 20 μL genotyping reaction contained 1X DurAmp mastermix (Life Technologies), 4 μL of DNA, 1X custom *CPT1A* p.P479L Taqman SNP genotyping assay (Life Technologies) *CPT1A* Probe and Primer Mix "CPT1A-CPT1, SNP AbD" (containing primers: GGCCTCAACGCTGAACACT (5'); GTGAAAACTCACCTCCCAAAGGT (3'); normal reporter: CPT1A-CPT1V2, CACGATCGGCGCATC, VIC; mutant reporter: CPT1A-CPT1M2, CACGATCAGCGCATC). PCR amplification was conducted using a on a ViiA7 real-time PCR system. Reaction conditions were 2 min at 50°C, 10 min at 95°C, followed by 40 thermal cycles of 15s at 95°C and 1min at 60°C. Sample genotype was determined using the ViiA7 real-time PCR software by analysing the allelic specific fluorescence data.

4.2.4 Statistical analysis

I used descriptive statistics to summarize differences in covariates and outcomes by *CPT1A* genotype. I conducted univariable tests of statistical significance using logistic regression to explore relationships between variables and outcomes and pairwise correlation tests to show the inter-relationships between the variables. I used complete case multivariable logistic regression to

examine association of CPT1A p.P479L variant with outcomes using two models: Model 1 (all outcomes) adjusted for community well-being index (CWB) and residence in Iqaluit for all outcomes. Model 2 (LRTI and RSV admission) adjusted for CWB, residence in Iqaluit, sex, preterm birth (PTB; <37weeks gestation), presence of major congenital anomalies, postnatal maternal smoking, breastfeeding ≥6mths and food insecurity. Model 2 (otitis media, gastroenteritis and dental interventions) adjusted for CWB, residence in Iqaluit, sex, PTB, postnatal maternal smoking, breastfeeding ≥6mths and food insecurity. Odds ratios with 95% confidence intervals were considered statistically significant for two-tailed p-values<0.05.

I conducted sensitivity analysis using multiple imputation by chained equations to create values for missing values for preterm birth (n=34), postnatal maternal smoking (n=408), breastfeeding ≥6 months (n=145) and food insecurity (n=455). All variables and outcomes were included in the imputation and 20 imputed data sets were created. Comparison of imputed data to complete case analysis was then performed. Hardy-Weinberg equilibrium (HWE) was analyzed using the $\chi 2$ test with $p<0.05$ significance level. Data were analysed using Stata 16SE [159].

4.3 RESULTS

Charts for 2523 Inuit children were reviewed. Charts without medical history (e.g. a single visit to health centre; n=60) were excluded. *CPT1A* genotype status was available for 2225/2463 records (90.3%); 110 of the 238 records without genotype were births that occurred in provinces outside the Nunavut newborn screening program. *CPT1A* genotype distribution was 68.7% p.P479L homozygous, 25.6% p.P479L heterozygous and 5.7% non-carrier wildtype (Table 4.1).

Table 4.1 Regional distribution of *CPT1A* p.P479L genotype in Inuit children born in Nunavut (2010-2013, n=2225)

	Total	Non-carrier Wildtype		p.P479L Heterozygous		p.P479L Homozygous		p.P479L allele 2010-13 Inuit births		p.P479L allele 2006 births[a]		
	n	n	freq	n	freq	n	freq	freq	(95%CI)	n	freq	(95%CI)
Nunavut	2,225	126	0.057	570	0.256	1,529	0.687	0.815 [b]	(0.805-0.828)	695	0.770 [b]	(0.747-0.792)
Kitikmeot	482	11	0.023	98	0.203	373	0.774	0.876	(0.853-0.896)	150	0.850	(0.804-0.888)
Kivalliq	754	51	0.068	214	0.284	489	0.649	0.791 [b]	(0.769-0.811)	243	0.827	(0.791-0.860)
Qikiqtaaluk	989	64	0.065	257	0.260	668	0.675	0.805 [b]	(0.788-0.823)	302	0.684 [b]	(0.645-0.721)
Iqaluit	250	40	0.160	110	0.440	100	0.400	0.620	(0.576-0.663)		n/a	

[a]Data from all live births in 2006 to women residing in Nunavut [20]
[b] Allele frequency not in Hardy-Weinberg equilibrium. *CPT1A*: Carnitine palmitoyltransferase 1A, 95%CI: 95% Confidence interval.

Table 4.2: Infant and maternal characteristics by *CPT1A* p.P479L genotype for Inuit children born in Nunavut (2010-2013, n=2225)

	Non-carrier Wildtype (n=126) n /total (%)	p.P479L Heterozygous (n=570) n /total (%)	p.P479L Homozygous (n=1529) n /total (%)	Total Cohort (n=2225) n /total (%)	Missing n (%)
Male	58/126 (46.0)	289/570 (50.7)	773/1529 (50.6)	1120/2225 (50.3)	0
Preterm (<37weeks)	13/124 (10.5)	67/565 (12.0)	186/1502 (12.4)	266/2191 (12.1)	34 (1.5)
mean GA	38.7wks	38.5wks	38.2wks	38.1wks	
Term LBW (<2500g)	0/123 (0)	6/560 (1.1)	33/1513 (2.2)	39/2196 (1.8)	29 (1.3)
mean birth weight	3526g	3456g	3344g	3341g	
Mat. age <20yrs	26/117 (22.2)	98/529 (18.5)	331/1421 (23.3)	455/2067 (22.0)	158 (7.1)
mean mat. age	24yrs	24yrs	24yrs	24yrs	
Breastfeeding ≥6mths	43/123 (35.0)	200/531 (37.7)	490/1426 (34.4)	733/2080 (35.2)	145 (6.5)
Postnatal mat smk.	61/94 (64.9)	384/460 (83.4)	1119/1263 (88.6)	1564/1817 (86.1)	408 (18.3)
Food insecurity <5yrs	21/93 (22.6)	149/450 (33.1)	577/1227 (47.0)	747/1770 (42.2)	455 (20.4)

CPT1A: Carnitine palmitoyltransferase 1A. Total: number of charts with data for category. Term LBW: Term low birth weight (37weeks gestation, <2500g), Mat. Age: maternal age, Mat. Smoke: Maternal postnatal smoking.

Table 4.3 Pairwise correlation coefficients between outcomes and variables

	LRTI <5yrs	RSV <5yrs	OM <5yrs	GE <5yrs	Dental <5yrs	p.P479L Hmz	p.P479L Het	CWB	Iqaluit	Male	PTB	CHDs	Other CAs	Mat. Smk	BF ≥6mth	Food Insecure
LRTI <5yr	1.00															
RSV <5yr	0.492**	1.00														
OM <5yr	0.080**	0.053*	1.00													
GE <5yr	0.091**	0.041*	0.146**	1.00												
Dental < 5yr	0.062*	0.012	0.070*	0.037	1.00											
p.P479LHmz	0.147**	0.052*	0.094*	0.098**	0.093**	1.00										
p.P479LHet	-0.118**	-0.035	-0.039	-0.069*	-0.028	-0.870**	1.00									
CWB	-0.053*	-0.012	-0.221**	-0.122**	-0.185**	-0.296**	0.181**	1.00								
Iqaluit	0.014	0.018	-0.235**	-0.064*	-0.109**	-0.217**	0.121**	0.790**	1.00							
Male	0.032	-0.006	-0.000	0.039	0.001	0.006	0.002	-0.018	-0.017	1.00						
PTB	0.144**	0.046*	-0.041*	-0.020	-0.018	0.008	-0.046*	-0.034	-0.008	0.0479*	1.00					
CHD	0.131**	0.044*	0.020	-0.012	0.046*	0.014	-0.044*	-0.042*	-0.024	-0.053*	0.087**	1.00				
Other CAs	0.087**	0.032	0.025	0.0001	0.003	0.033	-0.046*	-0.005	-0.014	0.044*	0.056*	0.032	1.00			
Mat. Smk	-0.112**	-0.019	-0.004	-0.039	-0.041*	-0.034	0.032	0.029	-0.020	-0.035	-0.077**	-0.035	-0.018	1.00		
BF ≥6mths	0.063*	0.024	0.041	0.007	0.040	0.110**	-0.033	-0.150**	-0.142**	0.021	0.025	0.005	0.006	-0.076*	1.00	
Food Insecure	0.063*	0.038	0.027	0.030	0.028	0.147**	-0.101**	-0.164**	-0.154**	0.014	-0.006	0.026	-0.038	0.016	0.146**	1.00

LRTI: lower respiratory tract infection, RSV: Respiratory syncytial virus, OM: Otitis media, GE: Gastroenteritis, Dental: major dental interventions (extractions, restorations, surgeries). p.P479L Hmz (LL): homozygous for the carnitine palmitoyltransferase 1A p.P479L variant, p.P479L Het (PL): heterozygous for the carnitine palmitoyltransferase 1A p.P479L variant, CWB: community well-being index, PTB: preterm birth (<37weeks gestation), CHD: presence of congenital heart defect, Other CAs: presence of other major congenital anomalies, Mat. Smk: postnatal maternal smoking, BF6mths+: breastfeeding 6 months or longer, FI: Food insecurity.
*: significant at p=0.05
**: significant at p=0.05 using Bonferroni correction for multiple testing

The p.P479L variant prevalence was highest in Kitikmeot (allele frequency: 0.876, 95%CI:0.853-0.896) and lowest in Kivalliq (allele frequency: 0.790, 95%CI:0.768-0.810). The p.P479L allele was in HWE in Kitikmeot and the town of Iqaluit, but not Kivalliq, Qikiqtaaluk or for the population of Nunavut as a whole.

There were no significant differences in birth related characteristics between *CPT1A* genotype groups (Table 4.2). Pairwise correlation analyses showed p.P479L homozygosity was positively correlated with all outcomes as well as postnatal maternal smoking and food insecurity and negatively correlated with CWB and residence in Iqaluit. Postnatal maternal smoking was positively correlated with food insecurity and negatively correlated with CWB, residence in Iqaluit and breastfeeding $\geq$6 months (Table 4.3).

Overall, 607 (27.3%) children were admitted to regional or tertiary hospital for LRTI (Table 4.4). Of those, 298 were tested for RSV and 182 tested positive, representing 8.2 % of children in the study (Figure 4.1). The proportion of children admitted for LRTI were 31.9% for p.P479L homozygotes, 18.4% for p.P479L heterozygotes and 11.9% for non-carrier wildtype. For infants, 449 (20.2%) were admitted for LRTI; of those, 255 were tested for RSV and 149 tested positive, representing 6.7% of infants. p.P479L homozygotes were significantly younger at first admission for LRTI than non-carriers (mean age: 8.6mths versus 15.4mths, p=0.025).

Table 4.4 Infectious illness by *CPT1A* p.P479L genotype in Inuit children born in Nunavut (2010-2013, n=2225)

	Cohort (n=2225)	**Non-carrier (n=126)**	**p.P479L Heterozygous (n=570)**		**p.P479L Homozygous (n=1529)**	
Outcome variable	**n (%)**	**n (%)**	**n (%)**	**cOR (95%CI)**	**n (%)**	**cOR (95%CI)**
LRTI admitted, 0-5yrs	607 (27.3)	15 (11.9)	105 (18.4)	1.7 (0.93-3.0)	487 (31.9)	3.5 (2.0-6.0)
LRTI admitted, infants (<1yr)	449 (20.2)	9 (7.1)	71 (12.5)	1.9 (0.89-3.8)	369 (24.1)	4.2 (2.1-8.3)
RSV admitted, 0-5yrs	182 (8.2)	3 (2.4)	39 (6.8)	3.0 (0.92-9.9)	140 (9.2)	4.1 (1.3-13.2)
RSV admitted, infants (<1yr)	149 (6.7)	3 (2.4)	31 (5.4)	2.4 (0.71-7.9)	115 (7.5)	3.3 (1.0-10.7)
Otitis media, 0-5yrs	1919 (86.3)	90 (71.4)	474 (83.2)	2.0 (1.3-3.1)	1355 (88.6)	3.1 (2.1-4.7)
Otitis media 3+ episodes, 0-5yrs	1290 57.2	48 (37.8)	274 (46.8)	1.4 (0.98-2.1)	954 (62.4)	2.8 (1.9-4.1)
Otitis media, infants (<1yr)	1413 (63.5)	54 (42.9)	320 (56.1)	1.7 (1.2-2.5)	1039 (67.9)	2.8 (2.0-4.1)
Gastroenteritis, 0-5yrs	1109 (49.8)	47 (37.3)	249 (43.7)	1.3 (0.87-1.9)	813 (53.1)	1.9 (1.3-2.8)
Gastroenteritis, infants (<1yr)	637 (28.6)	19 (15.1)	137 (24.0)	1.8 (1.1-3.0)	481 (31.5)	2.6 (1.6-4.3)
Dental interventions, 0-5yrs	794 (35.7)	22 (17.5)	188 (33.0)	2.3 (1.4-3.8)	584 (38.2)	2.9 (1.8-4.7)
Mean num. admits/illnesses	**mean (95% CI)**	**mean (95% CI)**	**mean (95% CI)**	**Coef. (p)**	**mean (95% CI)**	**Coef. (p)**
LRTI admits, 0-5yrs	0.42 (0.38-0.46)	0.15 (0.07-0.23)	0.24 (0.20-0.29)	0.09 (0.278)	0.51 (0.46-0.56)	0.36 (<0.001)
mean age 1st admit (mths)	9.0 (8.1-9.9)	15.4 (5.5-25.2)	12.0 (9.3-14.6)	-3.39 (0.280)	8.6 (7.7-9.6)	-6.72 (0.025)
Otitis media, 0-5yrs	4.08 (3.92-4.25)	2.38 (1.91-2.84)	3.00 (2.75-3.24)	0.62 (0.11)	4.63 (4.41-4.85)	2.25 (<0.001)
mean age at 1st episode (mths)	11.6 (11.2-12.1)	13.6 (11.2-16.2)	13.6 (12.5-14.7)	-0.02 (0.988)	10.8 (10.3-11.3)	-2.81 (0.015)
Gastroenteritis, 0-5yrs	0.93 (0.88-0.99)	0.61 (0.43-0.79)	0.73 (0.64-0.81)	0.12 (0.35)	1.04 (0.97-1.11)	0.43 (<0.001)
mean age at 1st episode (mths)	14.1 (13.4-14.8)	17.4 (13.6-21.2)	14.5 (12.9-16.0)	-2.94 (0.123)	13.8 (13.0-14.6)	-3.61 (0.044)

CPT1A: carnitine palmitoyltransferase 1A, cOR: crude odds ratio, CI: confidence interval, Coef: regression coefficient, LRTI: lower respiratory tract infection, RSV: Respiratory syncytial virus, Dental: major dental interventions (extractions, restorations, surgeries).

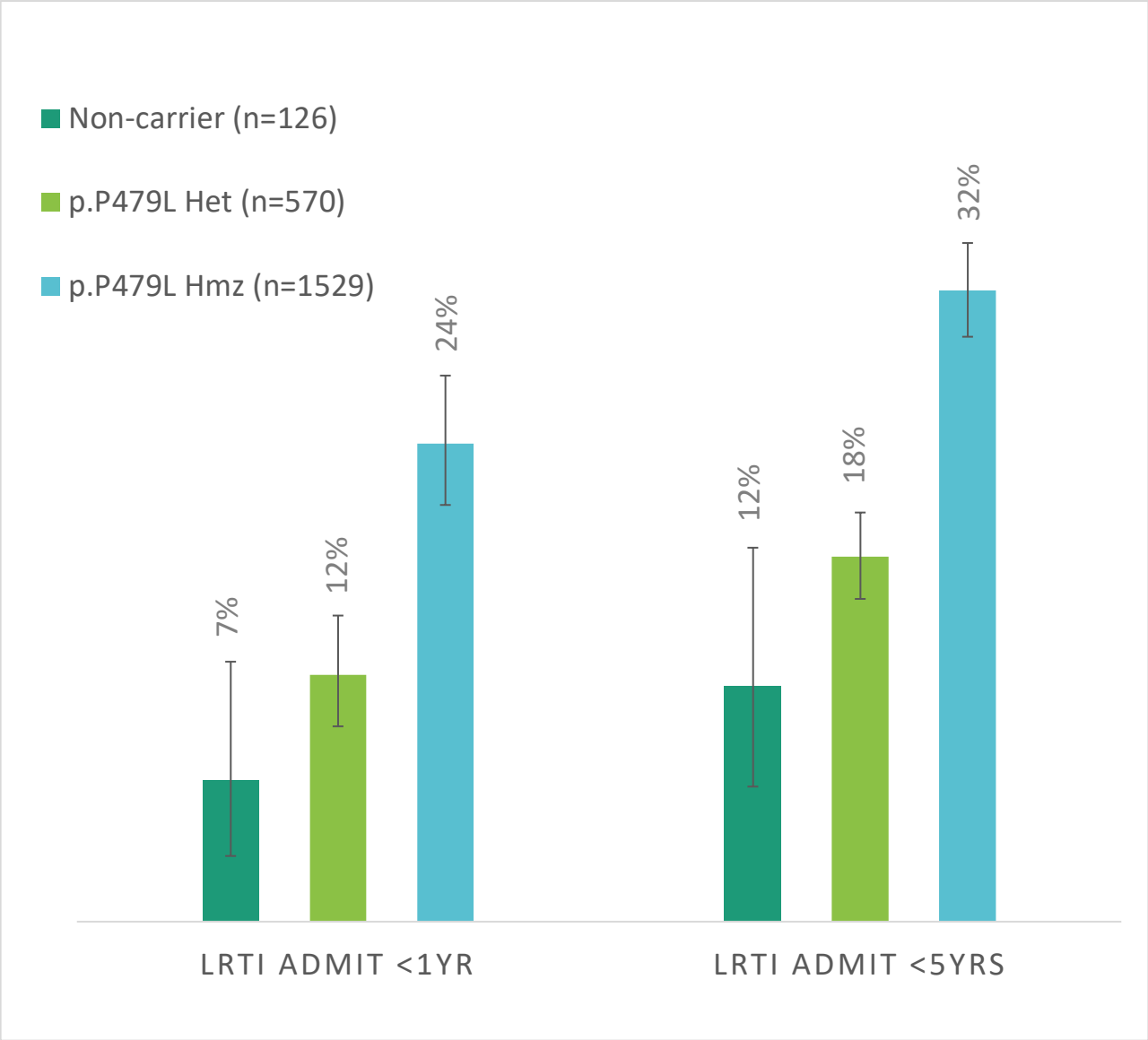

Figure 4.1 Children admitted for lower respiratory tract infection (LRTI) by *CPT1A* genotype
Proportion of infants (<1yr) and children (0-5yrs) admitted to hospital (regional or tertiary/out of territory) for lower respiratory tract infection (LRTI) by *CPT1A* genotype (n=2225). Non-carrier: non-carrier for the p.P479L variant, p.P479L Het: heterozygous for the p.P479L variant, p.P479L Hmz: homozygous for the p.P479L variant

Table 4.5 Multivariable logistic regression results for association of CPT1A p.P479L variant with infectious illness during infancy and early childhood in Inuit children residing in Nunavut (2010-2013)

	Early Childhood (0-5 years)				Infants (<1 year)			
	p.P479L Homozygous (LL)		p.P479L Heterozygous (PL)		p.P479L Homozygous (LL)		p.P479L Heterozygous (PL)	
	OR (95%CI)	p	OR (95%CI)	p	OR (95%CI)	p	OR (95%CI)	p
LRTI Admission								
Univariable	3.47 (2.00-6.01)	**<0.001**	1.66 (0.93-2.95)	0.082	4.15 (2.08-8.25)	**<0.001**	1.82 (0.89-3.76)	0.103
[a]Model 1	3.19 (1.82-5.60)	**<0.001**	1.62 (0.90-2.90)	0.101	3.28 (1.63-6.58)	**0.001**	1.64 (0.79-3.39)	0.182
[b]Model 2 (cc)	2.88 (1.46-5.64)	**0.002**	1.63 (0.81-3.29)	0.169	2.79 (1.29-6.03)	**0.009**	1.54 (0.69-3.44)	0.291
[b]Model 2 (imputed)	3.11 (1.75-5.52)	**<0.001**	1.64 (0.91-2.98)	0.102	3.26 (1.60-6.64)	**0.001**	1.69 (0.81-3.54)	0.161
RSV Admission								
Univariable	4.13 (1.30-13.15)	**0.016**	3.02 (0.92-9.92)	0.069	3.33 (1.04-10.64)	**0.042**	2.36 (0.71-7.85)	0.161
[a]Model 1	4.17 (1.29-13.47)	**0.017**	3.07 (0.93-10.13)	0.066	2.89 (0.89-9.36)	0.077	2.23 (0.67-7.43)	0.193
[b]Model 2 (cc)	3.04 (0.92-10.07)	0.068	2.61 (0.77-8.82)	0.122	2.02 (0.61-6.71)	0.249	1.79 (0.52-6.11)	0.355
[b]Model 2 (imputed)	4.12 (1.27-13.41)	**0.019**	3.11 (0.94-10.32)	0.064	2.81 (0.86-9.18)	0.087	2.23 (0.66-7.47)	0.194
Otitis Media								
Univariable	3.12 (2.05-4.73)	**<0.001**	1.97 (1.26-3.07)	**0.003**	2.83 (1.96-4.09)	**<0.001**	1.70 (1.15-2.51)	**0.008**
[a]Model 1	1.95 (1.25-3.06)	**0.004**	1.64 (1.03-2.61)	**0.036**	1.83 (1.23-2.70)	**0.003**	1.41 (0.94-2.12)	0.096
[c]Model 2 (cc)	1.83 (1.05-3.21)	**0.034**	1.67 (0.94-2.99)	0.081	1.87 (1.18-2.96)	**0.008**	1.53 (0.95-2.47)	0.084
[c]Model 2 (imputed)	1.96 (1.24-3.10)	**0.004**	1.64 (1.02-2.62)	**0.040**	1.90 (1.28-2.82)	**0.002**	1.44 (0.95-2.17)	0.082
Gastroenteritis								
Univariable	1.91 (1.31-2.78)	**0.001**	1.30 (0.87-1.93)	0.197	2.58 (1.57-4.26)	**<0.001**	1.79 (1.06-3.02)	**0.030**
[a]Model 1	1.62 (1.10-2.38)	**0.015**	1.21 (0.81-1.81)	0.344	2.00 (1.20-3.34)	**0.008**	1.61 (0.95-2.73)	0.078
[c]Model 2 (cc)	1.74 (1.09-2.77)	**0.020**	1.32 (0.81-2.13)	0.264	2.32 (1.23-4.39)	**0.010**	2.01 (1.04-3.87)	**0.037**
[c]Model 2 (imputed)	1.65 (1.11-2.44)	**0.013**	1.24 (0.83-1.86)	0.302	2.00 (1.19-3.36)	**0.009**	1.62 (0.95-2.77)	0.075
Dental Interventions								
Univariable	3.14 (1.98-5.00)	**<0.001**	2.37 (1.46-3.84)	**<0.001**				
[a]Model 1	2.23 (1.38-3.58)	**0.001**	2.06 (1.26-3.36)	**0.004**				
[c]Model 2 (cc)	2.11 (1.22-3.66)	**0.008**	1.88 (1.07-3.32)	**0.029**				
[c]Model 2 (imputed)	2.27 (1.41-3.67)	**0.001**	2.09 (1.27-3.41)	**0.003**				

[a]Adjusted for community socioeconomic status (CWB) and residence in Iqaluit.
[b]Adjusted for community socioeconomic status (CWB) and residence in Iqaluit, sex, preterm birth (<37weeks gestation), major congenital anomalies, postnatal maternal smoking, breastfeeding ≥6months and food insecurity. [c]Adjusted for community socioeconomic status (CWB) and residence in Iqaluit, sex, preterm birth, postnatal maternal smoking, breastfeeding ≥6months and food insecurity CPT1A: carnitine palmitoyltransferase 1A, OR: odds ratio, CI: confidence interval, LRTI: lower respiratory tract infection, RSV: Respiratory Syncytial Virus, Dental: major dental interventions (extractions, restorations, surgeries), cc: complete case analysis, n=1697.

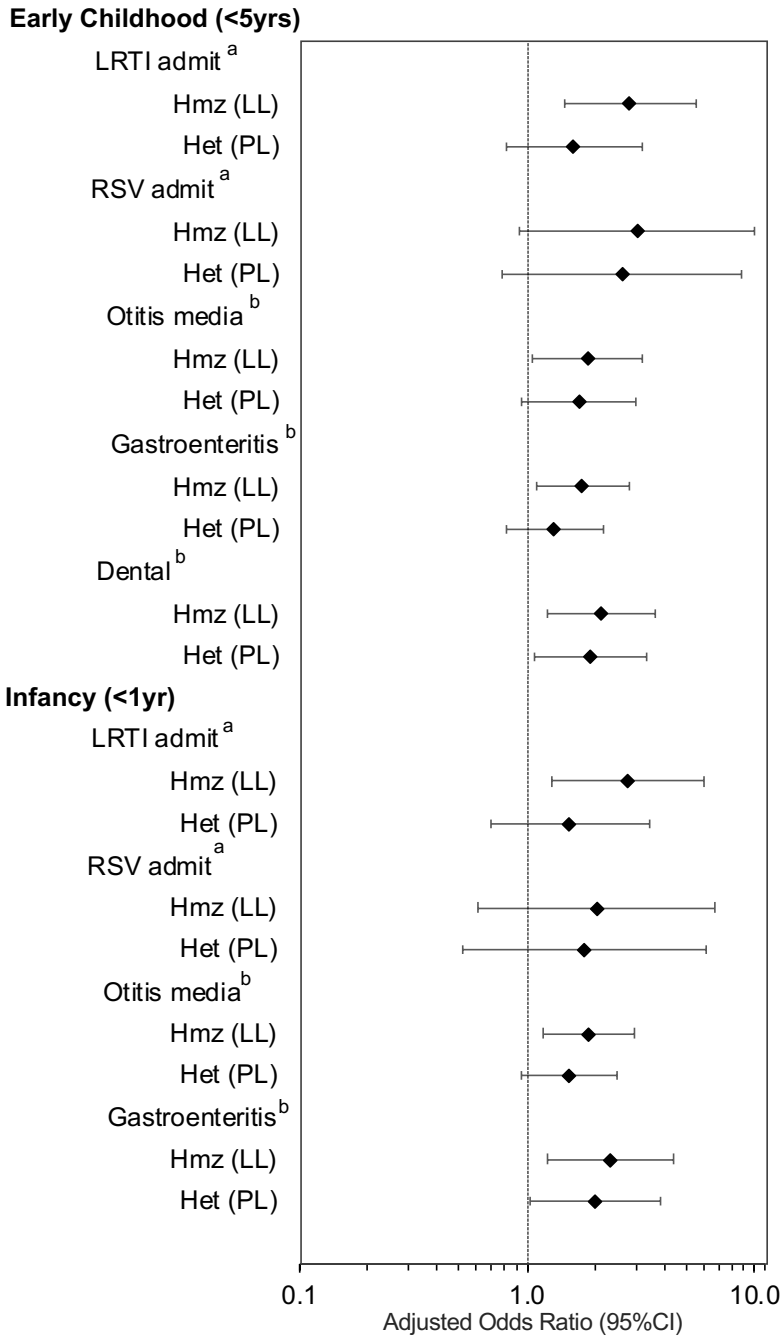

Figure 4.2 Carnitine palmitoyltransferase 1A (CPT1A) p.P479L variant and infectious illness by age group in Inuit infants from Nunavut (2010-2013, n=1697)

Hmz (LL): homozygous for the carnitine palmitoyltransferase 1A p.P479L variant. Het (PL): heterozygous for the carnitine palmitoyltransferase 1A p.P479L variant, LRTI: lower respiratory tract infection, RSV: Respiratory syncytial virus, Dental: major dental interventions (extractions, restorations, surgeries). CI: confidence interval. [a]Adjusted for community socioeconomic status (CWB) and residence in Iqaluit, sex, preterm birth (<37 weeks gestation), major congenital anomalies, postnatal maternal smoking, breastfeeding ≥6months and food insecurity. [b]Adjusted for community socioeconomic status (CWB) and residence in Iqaluit, sex, preterm birth, postnatal maternal smoking, breastfeeding ≥6months and food insecurity.

Results of univariable and multivariable logistic regression analysis are presented in Table 4.5. In univariable logistic regression analysis, *CPT1A* p.P479L homozygosity was associated with all outcomes and p.P479L heterozygosity was associated with otitis media and dental interventions and gastroenteritis in infancy. In Model 1 multivariable regression analysis adjusting for CWB and residence in Iqaluit, p.P479L homozygosity was associated with all outcomes except RSV admission in infancy and p.P479L heterozygosity remained associated with otitis media and dental interventions in early childhood but not gastroenteritis in infancy (see also Tables A.3.1-5, Sub-Appendix A.3).

Figure 4.2 shows the effect estimates for p.P479L homozygotes and heterozygotes after further adjustment for postnatal and socioeconomic variables (model 2). The adjusted ORs for p.P479L homozygotes were reduced but remained statistically significant for LRTI admission (aOR:2.88 95%CI:1.46-5.64), otitis media (aOR:1.83, 95%CI:1.05-3.21), gastroenteritis (aOR:1.74, 95%CI:1.09-2.77) and dental intervention (aOR:2.11, 95%CI:1.22-3.66) in early childhood. The effect estimate for RSV admission in early childhood was no longer statistically significant (aOR:3.04, 95%CI:0.92-10.07). p.P479L heterozygosity was associated with dental interventions (aOR:1.88, 95%CI:1.07-3.31) but the effect estimate for otitis media was no longer statistically significant (aOR:1.67, 95%CI:0.94-2.99). In infancy, p.P479L homozygosity was associated with LRTI admission (aOR:2.79, 95%CI:1.29-6.03), otitis media (aOR:1.87, 95%CI:1.18-2.96) and gastroenteritis (aOR:2.32, 95%CI:1.23-4.39) and p.P479L heterozygosity was associated with gastroenteritis (aOR:2.01, 95%CI:1.04-3.87).

To understand the impact of missing data, I conducted multiple imputation and compared model results to complete case analysis. The results were similar when the logistic regression models were run with imputation of missing values. All significant associations for p.P479L homozygosity were retained, and the effect estimates for p.P479L homozygosity with RSV admission and p.P479L heterozygosity with otitis media in early childhood no longer overlapped one (Table 4.5). However, the association of p.P479L heterozygosity with gastroenteritis in infancy was no longer statistically significant (see also Table A.3.6, Sub-Appendix A.3).

4.4 DISCUSSION

Previous studies have identified the CPT1A p.P479L variant as a possible risk factor for infectious illness in early childhood; however, those studies were small (≤427 children) and unable to adjust for confounding variables like breastfeeding, food security and community level well-being. My findings demonstrate that children homozygous for the CPT1A p.P479L variant had significantly higher rates of infectious illness compared to non-carrier wildtype, which was independent of sex, preterm birth, residence in Iqaluit, breastfeeding six months or longer, maternal smoking, food insecurity and CWB index (includes measures of individual community housing, education and income).

p.P479L homozygotes were almost three times more likely to be admitted to hospital for LRTI, which, with the exception of Iqaluit residents, require air transportation (either scheduled or emergency medical evacuation) representing significant illness. p.P479L homozygosity was associated with admission for RSV in model 1 (CWB index and Iqaluit residence) but not in the full model. Since only half of children with LRTI admissions had RSV test results documented,

the true prevalence of RSV admission may be underrepresented in this study, limiting interpretation of this result.

p.P479L homozygotes were almost twice as likely to have otitis media and gastroenteritis and require dental interventions in early childhood. Otitis media is associated with impaired hearing at five years of age and can have dramatic impacts on speech development and educational attainment [56–59]. In the study cohort, 86% of children had otitis media at least once, which is consistent with results for preschoolers from the Nunavut Inuit Child Health Survey [10] and 1.7 times the national average of 50% [54]. There are a number of risk factors associated with otitis media; however, after controlling for many of these factors, the association of p.P479L variant with otitis media remained statistically significant.

My results corroborate previous studies of the association of the p.P479L variant with child health outcomes in Alaska and BC. In their 2013 study of 427 Alaska Native infants, Gessner et al.[15] reported that p.P479L homozygosity was associated with increased risk of otitis media (aOR:3.0, 95%CI:1.8-5.1), LRTI admission (aOR:2.5, 95%CI:1.6-4.0) and admission for any reason (adjusting for maternal education, age, prenatal smoking and alcohol use, prenatal care and birth weight). However, when analysis was restricted to Northern and Western non-hub villages, where the variant is highly prevalent, only the association with otitis media remained statistically significant (aOR:3.6, 95%CI:1.4-8.9). The study used Medicaid data linked to birth certificate and newborn screening results. Those not enrolled in Medicaid were excluded from the study and postnatal exposures and SES indicators were not included in the analysis.

In a more recent study of 150 First Nations children from British Columbia, Sinclair et al.[18] found that children homozygous for the p.P479L variant were more likely to be admitted for LRTI (OR:6.0, 95%CI:1.6-22.4), otitis media (OR:13.5, 95%CI:1.5-109.4) and dental caries (OR:3.4, 95%CI:1.5-7.8) than those without the variant. There was also a trend towards intermediate risk for heterozygotes, although results were not statistically significant. While the study matched for location and year of birth, the study was unable to adjust for other factors present in the population. In the current analysis, adjustment for SES indicators, including food security and community level measures of education and housing, reduced but did not abolish the association of p.P479L variant homozygosity with LRTI admission, otitis media and dental interventions. I was also able to replicate the association reported for p.P479L heterozygotes with dental interventions. p.P479L heterozygosity was associated with LRTI admission and otitis media in model 1 (CWB index and Iqaluit residence); however, while the effect estimates still showed positive associations in the full model (model 2), the confidence intervals overlapped one.

Children homozygous for the *CPT1A* p.P479L variant may experience a more severe illness due to impaired ketogenesis but also impaired response of the immune system. As an enzyme critical for long chain fatty acid oxidation, CPT1A is important for energy homeostasis during fasting through ketogenesis and ATP production in the liver, as well as glucagon secretion in the pancreas [84] and T cell development and survival [131,132,134]. CD8+ T memory (Tmem) cells [131], especially resident Tmem cells [134], and CD4+ Th17 and Treg [132] cells have high demands for fatty acid oxidation and CPT1A activity. Currently, there is no evidence regarding whether the p.P479L variant impairs immune response and/or Tmem response to

repeat infection; however, a recent study found that mice expressing the *Cpt1a* p.P479L variant were resistant to the induction autoimmune encephalomyelitis (a mouse model of multiple sclerosis), possibly conferring protection through reduced lipid metabolism and/or through reduced peripheral T cell infiltration and subsequent impaired immune system activation [143].

The p.P479L variant was prevalent in Inuit children in Nunavut with an overall allele frequency of 0.82, ranging from 0.79 in Kivalliq to 0.88 in Kitikmeot. The allele frequency for Qikiqtaaluk (0.81) and for Nunavut overall were higher here than results from my previous study determining the prevalence of the variant in infants born in 2006 to women residing in Nunavut (Qikiqtaaluk: 0.68 and Nunavut: 0.77) [20]. In my previous study, I was unable to stratify results by ethnicity, so the higher frequencies reported here likely reflect that the current study includes Inuit children only.

The high prevalence of the p.P479L variant in Inuit populations suggests an historical advantage, where the variant flourished and became the major allele [20,21,116]. This speculation is supported by reports of strong positive selection signals at the site of the nucleotide change (rs80356779) [22,117,119,123] and evidence of protection for adverse lipid profiles in adults, including higher HDL-cholesterol and ApoA1 and reduced adiposity in Alaska [116,118]. Preliminary results from a recent Greenland study measuring fatty acid composition of red blood cell membranes showed interaction between traditional food intake and the CPT1A p.P479L variant, raising the possibility that this interaction may have influenced selection [223]. The p.P479L variant has also been associated with reduced height in Greenlandic Inuit (~2.1cm per p.P479L allele), which may be due to differences in fatty acid metabolites and their role in

growth hormone secretion [22]. The moderate insensitivity of p.P479L variant to malonyl-CoA, with residual activity in the fed state 4 times control (0.094 vs 0.023 nmol/min/mg), meaning a degree of fatty acid metabolism occurs even when carbohydrate is present [109]. This may have conferred an advantage for those utilizing a traditional "hunter's diet" rich in omega-3 marine-based fats with little or no carbohydrate [14,118].

There are a number of the socioeconomic status factors that are associated with childhood infectious illness present in Nunavut, including tobacco smoke exposure (prenatal and postnatal), household overcrowding and food insecurity [10,30,32,46,224]. Heavy prenatal smoking (10+ cigs/day) serves as a marker for low socioeconomic status and is associated with a number of adverse birth outcomes, including small for gestational age and low birth weight [30,179]. In the current cohort, 86% of women reported smoking postnatally and 17.5% of children lived in homes with three or more people/bedroom. In pairwise correlation tests, p.P479L homozygosity was significantly correlated with maternal postnatal smoking, food insecurity and CWB, suggesting that at least some of the risk associated with the p.P479L variant may be due to these underlying factors; however, p.P479L homozygosity remained significantly associated with LRTI admission, otitis media, gastroenteritis and dental interventions after adjustment for these variables.

4.5 LIMITATIONS

This was a retrospective chart review study. In the study cohort, 9% of records did not have *CPT1A* genotype information and were excluded from analysis. The CPT1A p.P479L variant was the only genetic variant studied and I cannot rule out that other genetic variants may have

contributed to the results. The p.P479L variant departed from HWE in two Nunavut regions, which may be due to the established positive selection for the variant [22,117,119], since selection can cause deviations of HWE, or to underlying population structure or other unknown contributors. The analysis was limited to Inuit children (as recorded on chart after self-identification); however, non-Inuit admixture could not be assessed in the study. Maternal education was poorly completed and could not be used in analysis.

4.6 CONCLUSION

Children homozygous for the p.P479L variant were more likely to be admitted for lower respiratory tract infections and were more likely to have otitis media, gastroenteritis and dental interventions, even after adjusting for perinatal, postnatal and socioeconomic variables. This study corroborates and expands on previous studies reporting increased rates of hospital admission for infectious illness for infants homozygous for the variant. Further studies are indicated to understand the impact of the CPT1A p.P479L variant on immune response to infection, information that will be important for the development of culturally relevant public health strategies in reducing childhood morbidity.

CHAPTER 5. DISCUSSION

5.1 SUMMARY OF DISSERTATION

In this dissertation, I investigated the role of the p.P479L variant of CPT1A in early child health, specifically neonatal hypoglycemia and high rates of infectious illness in early childhood in Nunavut. Infectious illness is a major concern in Nunavut, which has the highest national rates of infant hospital admissions for lower respiratory tract infection (LRTI) [4,6], and otitis media rate almost twice the national average [10,54] and an infant mortality rate four times the national average [9]. Children in Nunavut also experience high rates of tobacco smoke exposure, food insecurity and household crowding, all of which are important risk factors for infectious illness [3,5,10,32,156].

The p.P479L gene variant of carnitine palmitoyltransferase 1A (*CPT1A*) is prevalent in the Northern Indigenous populations of Alaska, Greenland and Canada, including Nunavut, where approximately 70% of infants born are homozygous for the variant [17,20–22]. The p.P479L variant has been identified as a possible contributor to adverse health outcomes of infants and children in Nunavut [12,14,18]. Since it was first described nearly twenty years ago [109], there has been increasing evidence of an association of the variant with early childhood morbidity and infant mortality, including hypoglycaemia in Alaska Native children [13], hypoglycemia and seizures in Nunavut Inuit children [14,23] and hospital admission for infection in early childhood in Alaska Native and BC First Nations children [15,18]. The variant has also been associated with sudden unexpected infant death and infant death due to infection in Alaska Native, Nunavut Inuit and BC First Nations infants [12,16,17].

Paradoxically, there have also been findings of protective effects against cardiovascular disease associated with the variant in Alaska Native and Greenlandic adults [116,118] and there is evidence of strong historical positive selection for the variant [22,117,119]. This has created uncertainty regarding the clinical significance of the variant in infant and child health [154], especially in populations where other risk factors for these outcomes are prevalent, including large distances to health care resources, food insecurity and household crowding [3,5,10,32]. This dissertation addresses the potential link between the p.P479L genetic variant and infant and child morbidity, within the context of social determinants of infant and child health outcomes in Nunavut.

This dissertation is based on the largest study to date of its kind evaluating the impact of the CPT1A p.P479L variant on the health status of Inuit children, revealing the principal finding that Inuit children homozygous for the *CPT1A* p.P479L variant have increased risk of infectious illness compared to non-carriers. Importantly, this association is independent of SES and other critical risk factors of infectious illness in infancy and early childhood.

Specifically, infants homozygous for the p.P479L variant were almost three times as likely to be admitted to hospital for LRTI and twice as likely to have otitis media and gastroenteritis and to require major dental interventions (restorations, extractions, treatment of infection, surgery) in early childhood. The association of the variant with infectious illness was independent of sex, preterm birth, residence in Iqaluit (the location of the only territorial hospital), breastfeeding six months or longer, maternal smoking, food insecurity and Statistics Canada community well-being (CWB) index, a continuous measure of community level socioeconomic status, including

household crowding, education and income. The CWB also indirectly measured remoteness, since the most remote communities of Nunavut also had the lowest CWB levels [222]. These results support and expand on previous studies, which, due to size (n≤427) and datasets used, were unable to include SES and other important variables, like remoteness [15,18].

My findings also suggest that newborns with the p.P479L variant may be at increased risk of hypoglycemia during the neonatal period. Newborns with inborn errors of metabolism, including fatty acid oxidation disorders like CPT1A deficiency, are at increased risk for hypoglycemia in the first days of life as they transition to postnatal life [197]. Although there was previous evidence of hypoglycemia in infancy and early childhood for p.P479L homozygotes [13,14], it was unknown if the variant conferred risk for hypoglycemia in the neonatal period. Other key findings were a higher incidence of neonatal hypoglycemia in healthy term Inuit newborns than expected in newborns without pre-existing risk factors (20% vs 10-14%) [191,198,199] and a significantly lower mean lowest blood glucose for newborns with the *CPT1A* p.P479L variant (both homozygotes and heterozygotes) compared to those without the variant (2.9 versus 3.2mmol/L). The adjusted ORs for developing neonatal hypoglycemia in healthy term newborns without other risk factors were 4.97 for *CPT1A* P479L homozygotes (95%CI:0.65-38.35) and 4.71 for P479L heterozygotes (95%CI:0.57-37.89). These results suggest the variant may impact energy homeostasis during newborn transition to postnatal life, but further research is needed to explore this risk. The findings of this study, described in Chapter 3, have been published in the journal Paediatrics and Child Health.

5.1.1 The CPT1A p.P479L variant, evidence for a clinical effect

The results reported in this dissertation add to the growing evidence for the clinical significance of the p.P479L variant in infancy and early childhood. As an enzyme critical for long chain fatty acid oxidation (LC-FAO), CPT1A is the critical first step in providing glucose-sparing energy and metabolites during fasting. Patients with FAO defects like CPT1A deficiency are at risk of hypoglycemia during the transition to postnatal feedings in the neonatal period [197,210] and hypoketotic hypoglycemia and metabolic decompensation during prolonged fasting or illness in infancy and early childhood [108]. In early childhood, infection is the main cause of metabolic decompensation for patients with inborn errors of metabolism [108].

Infants and children homozygous for the *CPT1A* p.P479L variant may have increased risk for hypoglycemia during prolonged fasting and may experience increased severity of infectious illness due to the combined impacts of impaired energy homeostasis in the liver and reduced glucagon secretion from pancreas [84]. Since glucagon secretion is dependent on CPT1A activity, stimulation of glycogen breakdown (glycogenolysis) and gluconeogenesis may be inadequate in those with the CPT1A p.P479L variant, which could further impair their ability to adapt to postnatal fast-feed cycles and to prolonged fasting during infancy and early childhood. There is also evidence that infectious illness can further impair LC-FAO in the liver through inhibitory signals from the hepatic innate immune system [225].

Infants and children with the variant may also have impaired adaptive immune response to infection, specifically memory T (Tmem) cell development and survival [131, 132,134]. Studies have shown that CD8+ T memory (Tmem) cells [131], especially resident Tmem cells [134], and

CD4+ Th17 and Treg [132] cells have high demands for fatty acid oxidation and CPT1A activity. There is currently no evidence that the p.P479L variant impairs the adaptive immune response to infection; however, there is recent evidence that *Cpt1a* p.P479L variant expressing mice are resistant to the induction of autoimmune encephalomyelitis (a mouse model of the autoimmune disease, multiple sclerosis) [143]. Combined with the low rate of multiple sclerosis reported for Inuit populations where the variant is prevalent [143], this is suggestive that the variant may influence immune system activation. T cell studies are underway at UBC (personal communication, B. Rakic) to determine if carriers have impaired function.

5.1.2 Evidence of a p.P479L heterozygote effect

CPT1A p.P479L heterozygotes had an intermediate incidence of neonatal hypoglycemia, falling between p.P479L homozygotes and non-carriers. As well, p.P479L heterozygous children were statistically more likely to require dental interventions and have gastroenteritis in infancy than those without the variant and also trended towards increased otitis media. This indicates a possible heterozygous effect, which is thought provoking since classic CPT1A deficiency is considered an autosomal recessive disorder. These findings could be reflective of a gradient effect of impaired ketogenesis, glucagon secretion and impaired immune system function for those heterozygous and homozygous for the variant.

My study is not the first to report this phenomenon, but supports earlier work carried out in BC First Nations on Vancouver Island by Sinclair et al.[18] of early childhood infectious illness (n=150), which also found that p.P479L heterozygotes showed a trend towards increased in hospitalization rates. Furthermore, Rajakumar et al.[116] found levels of HDL-cholesterol and

associated apoA-I in p.P479L heterozygotes that were intermediate between p.P479L homozygous and non-carriers. Finally, Skotte et al.[22] showed an intermediary heterozygote effect on height. Taken together, these results support a possible dosage effect in these outcomes.

The heterozygote effect may be explained by the evidence that CPT1A exists as a trimer or hexamer in the mitochondrial outer membrane (MOM) [96,97] and/or forms a complex with other MOM proteins, long chain acyl-CoA synthetase and the MOM voltage-dependent anion channel (also known as the mitochondrial porin) [98]. If both the wildtype and p.P479L variant form of the CPT1A enzyme are present in the complexes, this could lead to an intermediate level of CPT1A activity in the fasted state, falling between wildtype and p.P479L homozygous state activity levels. Intriguingly, this could also result in a residual CPT1A activity for p.P479L heterozygotes in the fed state as well.

5.1.3 Long term effects of the p.P479L variant

I report here that newborns with the variant (both homozygous and heterozygous) had higher incidence of transient asymptomatic neonatal hypoglycemia than those without the variant and they also had higher incidence then previously reported for healthy term infants [190]. Neonatal hypoglycemia is associated with serious neurodevelopmental effects [200,214,215], including a two to three-fold increased risk of impaired executive function and visual motor performance at four to five years of age [215]. However, the majority of studies into the long-term effects of neonatal hypoglycemia have focussed on newborns that are considered to be at-risk due to lower metabolic stores (e.g. glycogen) and glucose metabolic defects (e.g. PTB, SGA, LGA, maternal diabetes) [190]. It remains unclear whether asymptomatic transient neonatal hypoglycemia in

healthy term newborns represents a similar risk of long-term neurological effects. This is an area the needs attention.

Homozygosity for the CPT1A p.P479L variant was associated with infectious illness in infancy and early childhood including LRTI admission, otitis media and gastroenteritis. Infectious illness during early childhood can have several long-term effects. Severe and repeated LRTI illness in infancy and early childhood are associated with wheezing and asthma [51,52]. As well, LRTI is also associated with increased risk for otitis media, and recurrent and chronic otitis media can delay language development, lead to hearing loss and can have serious long-term impacts on mental health and well-being [56–59], which is a concern in Nunavut. Exposure to tobacco smoke and household crowding are risk factors for both LRTI and otitis media [53,226–229], and, as I presented here, highly prevalent in Nunavut. However, my results demonstrate that the risk of admission for LRTI and otitis media associated with the p.P479L variant were independent of those factors. Further research is needed to understand the underlying mechanisms of this association. Other infectious disease susceptibility throughout the life course (such as for tuberculosis) have yet to be explored in the context of the p.P479L allele.

5.2 LIMITATIONS

This study was the first and largest comprehensive cohort study including all three Nunavut regions to determine the association of the CPT1A p.P479L variant with early child health in Inuit children living in Nunavut. There are, however, a number of limitations to consider when reviewing these results.

This was a community-based chart review of medical charts for live births to Inuit women residing in Nunavut. Teams of chart reviewers travelled to 18 of the 25 Nunavut communities to collect perinatal, labour/delivery, newborn, well-baby and child health outcomes which were abstracted from medical charts in health centres, the territorial hospital in Iqaluit and at Iqaluit Public Health. All communities with more than 20 births per year were visited and greater than 80% of births to Nunavummiut during the study period were included. Seven communities with low birth rates (mean:10 births/year, range 2-20) were not visited due to time and travel constraints. Due to the nature of the study, stillbirths and terminated pregnancies were not ascertained and neonatal deaths that occurred out of territory are likely under-represented especially for neonatal deaths during the first hospitalization (for example extreme prematurity and severe congenital anomalies), which may impact ascertainment of congenital anomalies and neonatal deaths. Rates for these outcomes reported here may be lower than reported by Statistics Canada, which collects this data from all provinces and territories [9].

Information on medical investigations, laboratory test results and prenatal and postnatal exposures were taken from medical charts. Not all fields and forms were completed for all charts due to the limited community resources to document comprehensive medical data, including prenatal and postnatal exposure information. In Chapter 2, I provide information on smoking, vitamin use, country food consumption, food security and household crowding, which is based on self-reported information taken from prenatal and well-baby records. Although information for these variables were not available for all charts, the results I report here are similar to results of previously published data for smaller studies in Nunavut.

I was successful in linking *CPT1A* genotype for 90% (2225/2463) of the community-based chart review records (Chapter 4). Of the records that could not be linked, 46% (110/238) were for children born in surrounding provinces, outside the Nunavut newborn screening program and 9% (n=22) had missing maternal data. The *CPT1A* p.P479L variant was the only genetic variant studied and I cannot rule out that other genetic variants may have contributed to the results. The p.P479L variant departed from HWE in two Nunavut regions, possibly due to the established positive selection for the variant [22,117,119], to underlying population structure or to other unknown contributors. Population structure (also known as population admixture or stratification) occurs when there are subgroups within a population of interest that have differing allele frequencies and differing baseline risk for the outcome due to differences in ancestry [230]. Based on data from Nunavik, European admixture is likely between 8-13% in Canadian Inuit populations, with very low to no admixture in very remote communities [117,123].

To control for population stratification, I limited my analysis to Inuit children (as noted in chart for infant and/or mother) which demonstrated a low number of non-carriers of the variant (6%). The low number of non-carriers of the variant is an important limitation of the study, especially in the analysis of neonatal hypoglycemia (n=30, Chapter 3), which likely impacted identifying statistical significance for neonatal hypoglycemia in newborns with the p.P479L variant. However; the adjusted effect estimates for term newborns with no risk factors for hypoglycemia were 4.97 (95%CI:0.65-38.35) for p.P479L homozygotes and 4.71 (95%CI:0.59-37.89) for p.P479L heterozygotes. As well, the results for p.P479L homozygotes and p.P479L heterozygotes in the infectious disease study (Chapter 4) were not underpowered and led to statistically significant results. Therefore, although the estimates for neonatal hypoglycemia

included one in the confidence interval, this does not preclude the clinical significance of these results.

5.3 FUTURE DIRECTIONS

I report that the p.P479L variant was associated with infectious illness in early childhood; however, further studies are needed to determine the underlying mechanism for this association. It will be important to build on the results presented here to determine the functional consequences of the p.P479L variant in infant and child health, including neonatal hypoglycemia and infectious illness. It will also be important to determine the long-term effects of neonatal hypoglycemia in healthy term infants in this population. This could be addressed in a variety of ways, including prospective cohort, case control and model system studies to better characterise the biochemical significance of the variant as well as to clarify environmental factors that may affect the penetrance of the variant.

5.3.1 Neonatal hypoglycemia in Inuit newborns

Future investigations are needed to determine whether newborns with the CPT1A p.P479L variant are able to adequately respond to hypoglycemia given the reliance of glucagon secretion on CPT1A activity. As well, until now, research studies of the long-term effects of neonatal hypoglycemia have focussed on symptomatic neonatal hypoglycemia and asymptomatic transient neonatal hypoglycemia in newborns that are in ‘at-risk’ categories including, preterm birth, small and large for gestational age newborns and infants of diabetic mothers.

A prospective longitudinal study of neonatal hypoglycemia in healthy term Inuit newborns that included measuring glucagon levels and assessment of early childhood neurodevelopmental at two to five years of age would be important to both replicate and expand on my findings in Chapter 3. Such as study would also help to answer questions regarding whether the p.P479L variant impacts glucagon secretion. The Children with Hypoglycaemia and Their Later Development (CHYLD) study (described by McKinlay et al.[231]) conducted a similar study of the long-term impact of neonatal hypoglycemia in 528 late-preterm and term neonates in at-risk categories. The study screened neonates using standard screening intervals but also measured blood glucose using masked interstitial continuous glucose monitoring (CGM). Children in the study were assessed for neuropsychological development assessment at two and four to five years [215]. A similar prospective longitudinal study in Nunavut with standard blood glucose screening conducted in tandem to glucagon testing, with long-term follow up of neurodevelopment could help to determine the true incidence of low blood sugar in Inuit neonates and the role of the p.P479L variant.

5.3.2 Exploration of the impact of the p.P479L variant on immune function

Many questions remain regarding the underlying mechanisms driving the association of the p.P479L variant with infectious illness in infancy and early childhood, which may be due to impaired CPT1A response to intercurrent illness but may also involve CPT1A function in other tissues including the pancreas [84] and the adaptive immune system, including memory T cell development and survival [131,132,134]. The role of immune function in mediating the association of the p.P479L variant with infectious illness could be explored in a number of ways.

The proposed prospective study on neonatal hypoglycemia could be expanded to include assessment of infectious illness and T cell function studies to compare the metabolic profiles of all genotypes. Alternatively, a smaller study with children from all three genotypes (p.P479L homozygotes, heterozygotes and non-carriers) looking at memory T cell response to antigens could help to determine if the p.P479L variant impacts adaptive immune response to common viral pathogens, including RSV.

The *Cpt1a* p.P479L homozygous mouse model described by Mørkholt et al.[143] could help to further characterize the variant, including malonyl-CoA binding affinity, glucagon secretion, immune function and the impact of diet on *Cpt1a* expression and activity in liver and other tissues. Immune functions studies could include response to specific infectious pathogens like RSV and TB as well as the novel coronavirus, COVID-19. The *Cpt1a* p.P479L mouse model studies could help to understand whether the p.P479L variant represents an increased susceptibility for severe illness with COVID-19 infection and how the variant impacts inflammatory response during infection. The p.P479L *Cpt1a* mouse model could also help to determine the presence of increased sensitivity to fasting and fever.

There has recently been controversy regarding the dependence of memory T cells on FAO and CPT1A for long term survival [232,233]. The case-control and mouse model studies I describe above could help to answer these questions regarding the reliance of Tmem and other lymphocytes on CPT1A for development and survival. This model could also help investigate the impact of a diet high in omega-3 fatty acids like the traditional Inuit diet.

5.3.3 The role of diet with the p.P479L variant

There are a number of hypotheses as to why the variant has become the major allele in the population, which have focussed on the interaction of the traditional Inuit diet and the unique properties of the variant, including lower overall production of ketones, the ability to maintain a keto-adaptive state during seasonal changes in diet [14,18,116,119] and a protective effect of a diet high in omega-3 fatty acids that would increase hepatic expression of *CPT1A*, resulting in higher overall CPT1A activity [20,234]. It is possible that a combination of these hypotheses is at play.

For newborns and infants, breastfeeding combined with the traditional diet high in omega-3 fatty acids may have been sufficient to override the negative effects of the reduced CPT1A activity. The traditional Inuit practice of breastfeeding their children until they were three or five years of age [177], combined with a diet high in omega-3 fatty acids may have been protective against any deleterious effects of the variant. Although there have been reports that breastfeeding is lower in Inuit women than the national average [176], I found that among infants not undergoing custom adoption, breastfeeding was similar to national averages and one in three women breastfed for 12 months or longer. However, my data did not capture type of breastfeeding or information on maternal diet. Since the 1950's, country foods are no longer a primary food source for many Inuit women (11% of total dietary energy) and marine based omega-3 fatty acids now only comprise 18.5% of total PUFAs in the diet [127]. Further study on the interaction of diet and breastfeeding with the p.P479L variant, including exclusive versus partial breastfeeding and the interplay with maternal diet and infant health would allow better understanding how diet and breastfeeding impact infant health in those with the p.P479L variant.

5.3.4 Infant death and the p.P479L variant

In my previous review of infant mortality in Nunavut from 1999 to 2011, I found the majority of post-neonatal infant deaths in Nunavut were attributed to preventable causes such as SIDS/SUDI (55%) and infectious disease (31%), at proportions that were two and three times greater than the national averages [64]. In the previous study, I also determined that infants homozygous for the p.P479L variant had a moderate but significant increased risk for sudden unexpected death (SIDS/SDUI) and death die to infection, which was consistent with results from studies in BC First Nations and Alaska Native populations [16]. However, due to a lack of population level data, I was unable to include other risk factors in my analysis like sleep environment and tobacco smoke exposure. Here, I report that the rate of SIDS and SUDI remains high in the infants born between 2010 and 2013. A follow up study using the population level data from the current cohort for sleep environment and other risk factors could help determine if the previously reported risk associated with the variant for SIDS, SUDI and death due to infection are independent of these factors.

In 2016/17, the Government of Nunavut started a baby box initiative, which encourages early prenatal care and promotes safe sleep environments and breastfeeding [174]. A study on the current rates of SIDS and SUDI since the initiation of the baby box program could help evaluate the effectiveness of these public health efforts to encourage safe sleep positioning and other sleep practices to reduce SIDS and SUDI.

5.4 CONCLUSION

My results demonstrate that p.P479L variant is associated with infectious illness in infancy and early childhood; specifically, hospital admission for LRTI, otitis media, gastroenteritis and dental interventions (including surgeries and extractions prior to five years of age), after adjusting for perinatal, postnatal and socioeconomic variables. These results replicate and expand on previous studies reporting increased rates of hospital admission for infectious illness for infants homozygous for the variant. My research also determined that healthy term Inuit newborns from Kivalliq have an incidence of neonatal hypoglycemia of 20%, similar to that for newborns considered at-risk for neonatal hypoglycemia and that newborns with the p.P479L variant had higher incidence of neonatal hypoglycemia than newborns without the variant.

The high rates of adverse child health outcomes presented here represent significant early childhood morbidity and long-term impacts on health for Nunavummiut. There are many risk factors associated with these outcomes that are common in Nunavut, including crowded housing and food insecurity, which were common in this study.

With the onset of the 2019 global coronavirus pandemic, we are facing a new era of understanding the toll that viral infections can take on at-risk populations. Improved surveillance and treatment for infectious illness in Nunavut are important in reducing infectious illnesses [235,236]. The combination of comprehensive territorial smoking cessation programs with increased measures to control the spread of infectious illness and improved housing and food access could have dramatic impacts on reducing infectious illness in the entire population by limiting exposure to these pathogens and susceptibility to severe infection [60]. Much like

placing infants to sleep on their backs can override many underlying susceptibility to SIDS [69], controlling the spread of viral and bacterial pathogens would protect all Nunavummiut, including those with underlying susceptibilities, like the proposed increase susceptibility caused the p.P479L variant.

The timeliness of these results demonstrates the importance of understanding how a viral pandemic could impact those with the p.P479L variant in the context of remoteness of Nunavut communities. Multidisciplinary local input is indicated to determine if routine neonatal glucose screening and/or other management is indicated for Inuit infants. Further studies are needed to understand the role of the p.P479L variant in infection susceptibility, immune and inflammatory response and vaccination effectiveness in Inuit communities.

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APPENDIX A

A.1 SUB-APPENDIX

NUNAVUT WELL-BABY RECORD

EVIDENCE-BASED INFANT/CHILD HEALTH MAINTENANCE GUIDE:

2 MONTHS OLD

Surname	Given Name
Date of Birth DD MM YYYY / ☐ M ☐ F	Infant HCP#
Information Source (and relation)	
Contact Name (if different)	Contact Phone Number
Home Community/Health Centre	

Birth Mother Name (required)	Birth Mother HCP# (required)	Birth Father Name (optional)
Birth Place	Baby Surname at Birth	Birth Weight (g)

PAST PROBLEMS / RISK FACTORS / FAMILY HISTORY:

☐ TB Exposure

Age at Visit _____wks ____dys

Current Family: ☐ Birth family ☐ Adopted ☐ Foster care

☐ Guardian care changed since birth

Foster/Adopted Parents:_____

PARENT / GUARDIAN CONCERNS:

Length (cm)	Weight (g)	HC (cm)
%	%	%

NUTRITION (SINCE BIRTH)

Do You Currently Breastfeed? *(only check one)*

☐ Never Breastfed

☐ No, Discontinued at: _____ mths

☐ Yes, Breast milk **only** → Since: ☐ birth ☐ 7 days ago ☐ other: _____

☐ Yes, Breast milk **and other feeds** (including water) → In the past 7 days, how many feeds of other liquids/food per day? ☐ 1-2 ☐ ≥3

☐ Good Latch ☐ Nutritive Suck

Comments:

Other Liquids Introduced: ☐ No ☐ Yes → at _____ wks

Infant formula ☐ No ☐ Yes → Iron-fortified ☐ No ☐ Yes

Cow's milk ☐ No ☐ Yes ☐ Unknown

Other (tea, pop, etc) ☐ No ☐ Yes (specify) _____

Vitamin D Supplementation:

Do you have Vit. D drops at home? ☐ No ☐ Yes

If Yes: Are they given to baby?

☐ Never ☐ Sometimes ☐ Daily → Amt given: _____IU

Since your baby was born:

Were there times when the food for you and your family just did not last and there was no money to buy enough food?

☐ Never ☐ Sometimes ☐ Often ☐ Don't know/Refused

Have you been to CPNP? ☐ No ☐ Yes ☐ CPNP not available

ENVIRONMENT

Maternal Smoking: ☐ No ☐ Yes → Amount (cig/day): _____

Location of smoking: ☐ Inside ☐ Outside

People smoking inside the house: _____

People in house: _____ # Bedrooms in house: _____

Substance use in household: ☐ No ☐ Yes ☐ Don't know/Refused

Do you have any concerns about your baby's safety? ☐ No ☐ Yes

Nurse suspects abuse: ☐ No ☐ Yes ☐ Unsure

Social services involved: ☐ No ☐ Yes ☐ Unknown

Sleep Practices:

What position do you put baby to sleep in?

☐ back (supine) ☐ stomach (prone) ☐ side ☐ other: _____

Where does baby sleep?

☐ crib ☐ child bed ☐ foam mattress ☐ adult bed ☐ mattress on floor ☐ sofa ☐ other: _____

Does baby sleep alone/in own bed? ☐ No ☐ Yes ☐ Sometimes

→ Baby shares with: _____

PHYSICAL EXAMINATION / MEDICAL HISTORY

N = **N**ormal

A = **A**bnormal

	N	A
Fontanelles	☐	☐
Eyes (red reflex)	☐	☐
Corneal light reflex	☐	☐
Hearing inquiry/screening	☐	☐
Heart	☐	☐
Hips	☐	☐
Muscle tone	☐	☐
Reflexes	☐	☐

Developmental Assessment: Parental concern about delay: ☐ No ☐ Yes

Tool used: _____ *(note concerns below in 'Assessment')*

SINCE BIRTH: ☐ *Birth Defect Reporting Form completed*

Birth Defects detected: _____

Seizures: ☐ No ☐ Yes

If Yes:

Meds required ☐ No ☐ Yes

w/ Fever ☐ No ☐ Yes ☐ Unknown

w/ Low blood sugar ☐ No ☐ Yes ☐ Unknown

Lung Infections: # Admissions: _____

Admission to: ☐ Health centre ☐ Regional hospital ☐ Tertiary centre ☐ ICU ☐ Unknown

Type(s): ☐ Pneumonia ☐ Bronchiolitis ☐ TB ☐ Other

ASSESSMENT

Include notes on abnormal findings

☐ Well infant ☐ Needs follow-up ☐ Needs referral

VACCINES UP-TO-DATE: ☐ No ☐ Yes ☐ Unknown *(follow Nunavut Immunization Guide)*

SIGNATURE:

DATE: DD MM YYYY

Version 2.0 (Sep 2011) Adapted, modified, reproduced and used by the Government of Nunavut from the Rourke Baby Record (© Leslie Rourke, James Rourke and Denis Leduc, 2009) with the permission of the authors.

Blue Writing: Indicates Questions NOT to be answered by the parent/guardian

CONTINUED ON REVERSE

WHITE: CHILD'S CHART YELLOW: NUTAQQAVUT HEALTH INFORMATION SYSTEM (IQALUIT)

Figure A.1.1 Nunavut well-baby record, 2 months

NUNAVUT WELL-BABY RECORD

EVIDENCE-BASED INFANT/CHILD HEALTH MAINTENANCE GUIDE:

6 MONTHS OLD

Surname	Given Name
Date of Birth *DD MM YYYY*	☐ M ☐ F — Infant HCP#
Information Source (and relation)	
Contact Name (if different)	Contact Phone Number
Home Community/Health Centre	

Birth Mother Name (required)	Birth Mother HCP# (required)	Birth Father Name (optional)
Birth Place	Baby Surname at Birth	Birth Weight (g)

PAST PROBLEMS / RISK FACTORS / FAMILY HISTORY:

☐ TB Exposure

Current Family: ☐ Birth family ☐ Adopted ☐ Foster care
☐ Guardian care changed since 2 months old
Foster/Adopted Parents:_____

PARENT / GUARDIAN CONCERNS:

Length (cm)	Weight (g)	HC (cm)
%	%	%

NUTRITION (SINCE 2 MONTHS OLD)

Do You Currently Breastfeed? *(only check one)*
☐ Never Breastfed
☐ No, Discontinued at: _____ mths
☐ Yes, Breast milk **only** → Since: ☐ birth ☐ 7 days ago ☐ other: _____
☐ Yes, Breast milk **and other feeds** (including water) → In the past 7 days, how many feeds of other liquids/food per day? ☐ 1-2 ☐ ≥3

☐ Good Latch
☐ Nutritive Suck

Complementary/Solid Foods
Introduced: ☐ No ☐ Yes → at _____ mths

Iron Rich Foods:			Age started:
Infant cereal	☐ No	☐ Yes	_____ mths
Traditional meat	☐ No	☐ Yes	_____ mths
Other meat	☐ No	☐ Yes	_____ mths

Other Liquids Introduced: ☐ No ☐ Yes → at _____ mths
Infant formula ☐ No ☐ Yes → Iron-fortified ☐ No ☐ Yes
Cow's milk ☐ No ☐ Yes ☐ Unknown
Other (tea, pop, etc) ☐ No ☐ Yes (specify) _____

Vitamin D Supplementation:
Do you have Vit. D drops at home? ☐ No ☐ Yes
If Yes: Are they given to baby? ☐ Never ☐ Sometimes ☐ Daily
Rickets Diagnosis: ☐ No ☐ Yes ☐ Unknown → Amt given: _____IU

Since your baby was 2 months old:
Were there times when the food for you and your family just did not last and there was no money to buy enough food?
☐ Never ☐ Sometimes ☐ Often ☐ Don't know/Refused
Have you been to CPNP? ☐ No ☐ Yes ☐ CPNP not available
Has your baby attended an early childhood care program? ☐ No ☐ Yes (specify): _____

ENVIRONMENT

Maternal Smoking: ☐ No ☐ Yes → Amount (cig/day): _____
Location of smoking: ☐ Inside ☐ Outside
People smoking inside the house: _____
People in house: _____ # Bedrooms in house: _____
Substance use in household: ☐ No ☐ Yes ☐ Don't know/Refused
Do you have any concerns about your baby's safety? ☐ No ☐ Yes
Nurse suspects abuse: ☐ No ☐ Yes ☐ Unsure
Social services involved: ☐ No ☐ Yes ☐ Unknown

Sleep Practices:

What position do you put baby to sleep in?
☐ back (supine)
☐ stomach (prone)
☐ side ☐ other: _____

Where does baby sleep?
☐ crib ☐ child bed
☐ foam mattress ☐ adult bed
☐ mattress on floor ☐ sofa
☐ other: _____

Does baby sleep alone/in own bed? ☐ No ☐ Yes ☐ Sometimes
→ Baby shares with: _____

PHYSICAL EXAMINATION / MEDICAL HISTORY

N = **N**ormal
A = **A**bnormal

	N	A
Fontanelles	☐	☐
Eyes (red reflex)	☐	☐
Corneal light reflex	☐	☐
Cover-uncover test & inquiry	☐	☐
Hearing inquiry/screening	☐	☐
Heart	☐	☐
Hips	☐	☐
Muscle Tone	☐	☐
Reflexes	☐	☐

Developmental Assessment: Parental concern about delay: ☐ No ☐ Yes
Tool used: _____
General development delay 'Impression' ☐ None ☐ Mild ☐ Moderate ☐ Severe
Speech/language delay 'Impression' ☐ None ☐ Mild ☐ Moderate ☐ Severe
Referred for support: ☐ P.T. ☐ O.T. ☐ Speech ☐ Other
Diagnosed developmental condition: _____

SINCE 2 MONTHS OLD: ☐ *Birth Defect Reporting Form completed*
Birth Defects detected: _____

Seizures: ☐ No ☐ Yes
If Yes:
Meds required ☐ No ☐ Yes
w/ Fever ☐ No ☐ Yes ☐ Unknown
w/ Low blood sugar ☐ No ☐ Yes ☐ Unknown

Lung Infections: # Admissions: _____
Admission to:
☐ Health centre
☐ Regional hospital
☐ Tertiary centre
☐ ICU ☐ Unknown
Type(s):
☐ Pneumonia
☐ Bronchiolitis
☐ TB
☐ Other

ANEMIA SCREENING

Hgb (fingerprick): _____
If needed, do venipunc
Hgb (venipunc): ☐ Done ☐ Not done

Lab Results: *(if venipunc - fill in later)*
Hgb _____
MCV _____ Ferritin _____ CRP _____

SINCE BIRTH:
Iron prescribed: ☐ No ☐ Yes
Iron taken: ☐ No ☐ Yes ☐ Sometimes

ASSESSMENT
Include notes on abnormal findings

☐ Well infant ☐ Needs follow-up ☐ Needs referral

SIGNATURE:

DATE: *DD MM YYYY*

VACCINES UP-TO-DATE: ☐ No ☐ Yes ☐ Unknown *(follow Nunavut Immunization Guide)*

Blue Writing: Indicates Questions NOT to be answered by the parent/guardian

CONTINUED ON REVERSE

WHITE: CHILD'S CHART YELLOW: NUTAQQAVUT HEALTH INFORMATION SYSTEM (IQALUIT)

Figure A.1.2 Nunavut well-baby record, 6 months

NUNAVUT WELL-BABY RECORD

EVIDENCE-BASED INFANT/CHILD HEALTH MAINTENANCE GUIDE:

12 MONTHS OLD

Surname	Given Name
Date of Birth DD MM YYYY	☐ M ☐ F — Infant HCP#
Information Source (and relation)	
Contact Name (if different)	Contact Phone Number
Birth Mother HCP#	Home Community/Health Centre

PAST PROBLEMS / RISK FACTORS / FAMILY HISTORY:

Age at Visit _____ mths _____wks

☐ TB Exposure

Current Family: ☐ Birth family ☐ Adopted ☐ Foster care
☐ Guardian care changed since 6 months old
Foster/Adopted Parents:_____

PARENT / GUARDIAN CONCERNS:

Length (cm)	Weight (g)	HC (cm)
%	%	%

NUTRITION (SINCE 6 MONTHS OLD)

Do You Currently Breastfeed? *(only check one)*
☐ Never Breastfed
☐ No, Discontinued at: _____ mths
☐ Yes, Breast milk **only** → Since: ☐ birth ☐ 7 days ago ☐ other: _____
☐ Yes, Breast milk **and other feeds** (including water) → In the past 7 days, how many feeds of other liquids/food per day? ☐ 1-2 ☐ ≥3

☐ Good Latch
☐ Nutritive Suck

Complementary/Solid Foods
Introduced: ☐ No ☐ Yes → at _____ mths

Iron Rich Foods:			Age started:
Infant cereal	☐ No	☐ Yes	_____ mths
Traditional meat	☐ No	☐ Yes	_____ mths
Other meat	☐ No	☐ Yes	_____ mths

Other Liquids Introduced: ☐ No ☐ Yes → at _____ mths

Infant formula	☐ No	☐ Yes	→ Iron-fortified ☐ No	☐ Yes
Cow's milk	☐ No	☐ Yes		☐ Unknown
Other (tea, pop, etc)	☐ No	☐ Yes (specify) _____		

Vitamin D Supplementation:
Do you have Vit. D drops at home? ☐ No ☐ Yes
If Yes: Are they given to baby? ☐ Never ☐ Sometimes ☐ Daily
Rickets Diagnosis: ☐ No ☐ Yes ☐ Unknown → Amt given: _____IU

Since your baby was 6 months old:
Were there times when the food for you and your family just did not last and there was no money to buy enough food?
☐ Never ☐ Sometimes ☐ Often ☐ Don't know/Refused
Have you been to CPNP? ☐ No ☐ Yes ☐ CPNP not available
Has your baby attended an early childhood care program? ☐ No ☐ Yes (specify): _____

DENTAL

Is baby drinking from a cup? ☐ No ☐ Yes
From a bottle? ☐ No ☐ Yes
How often is a bottle taken to bed, excluding water?
☐ Never ☐ < Daily ☐ Daily ☐ > Daily

Teeth brushing frequency: ☐ < Daily ☐ Daily ☐ > Daily
Tooth extractions: ☐ No ☐ Yes
Oral assessment: ☐ Healthy ☐ Unhealthy
Tooth decay (including white spots): ☐ No ☐ Yes

ENVIRONMENT

Maternal Smoking: ☐ No ☐ Yes → Amount (cig/day): _____
Location of smoking: ☐ Inside ☐ Outside
People smoking inside the house: _____
People in house: _____ # Bedrooms in house: _____

Substance use in household: ☐ No ☐ Yes ☐ Don't know/Refused
Do you have any concerns regarding your baby's safety? ☐No ☐ Yes
Nurse suspects abuse: ☐ No ☐ Yes ☐ Unsure
Social services involved: ☐ No ☐ Yes ☐ Unknown

PHYSICAL EXAMINATION / MEDICAL HISTORY

N = **N**ormal
A = **A**bnormal

	N	A
Fontanelles	☐	☐
Eyes (red reflex)	☐	☐
Corneal light reflex	☐	☐
Cover-uncover test & inquiry	☐	☐
Hearing inquiry/screening	☐	☐
Tonsil size / Teeth	☐	☐
Heart	☐	☐
Hips	☐	☐

Developmental Assessment: Parental concern about delay: ☐ No ☐ Yes
Tool used: _____
General development delay 'Impression' ☐ None ☐ Mild ☐ Moderate ☐ Severe
Speech/language delay 'Impression' ☐ None ☐ Mild ☐ Moderate ☐ Severe
Referred for support: ☐ P.T. ☐ O.T. ☐ Speech ☐ Other
Diagnosed developmental condition: _____

SINCE BIRTH: Chronic draining ears: ☐ No ☐ Yes
times Antibiotics taken for ear infections: _____

SINCE 6 MONTHS OLD: ☐ *Birth Defect Reporting Form completed*
Birth Defects detected: _____
Seizures: ☐ No ☐ Yes → If Yes: Meds required ☐ No ☐ Yes
w/ Fever ☐ No ☐ Yes ☐ Unknown
w/ Low blood sugar ☐ No ☐ Yes ☐ Unknown

Lung Infections: # Admissions: _____
Admission to: ☐ Health centre ☐ Regional hospital ☐ Tertiary centre ☐ ICU ☐ Unknown
Type(s): ☐ Pneumonia ☐ Bronchiolitis ☐ TB ☐ Other

ANEMIA SCREENING

Hgb (fingerprick): _____
If needed, do venipunc
Hgb (venipunc): ☐ Done ☐ Not done

Lab Results: *(if venipunc - fill in later)*
Hgb _____
MCV _____ Ferritin _____ CRP _____

SINCE 6 MONTHS OLD:
Iron prescribed: ☐ No ☐ Yes
Iron taken: ☐ No ☐ Yes ☐ Sometimes

ASSESSMENT
Include notes on abnormal findings

☐ Well infant ☐ Needs follow-up ☐ Needs referral

VACCINES UP-TO-DATE: ☐ No ☐ Yes ☐ Unknown *(follow Nunavut Immunization Guide)*

SIGNATURE:

DATE: DD MM YYYY

Blue Writing: Indicates Questions NOT to be answered by the parent/guardian

CONTINUED ON REVERSE

WHITE: CHILD'S CHART YELLOW: NUTAQQAVUT HEALTH INFORMATION SYSTEM (IQALUIT)

Figure A.1.3 Nunavut well-baby record, 12 months

NUNAVUT WELL-BABY RECORD

EVIDENCE-BASED INFANT/CHILD HEALTH MAINTENANCE GUIDE:

2 – 3 YEARS OLD

Surname	Given Name

Date of Birth DD MM YYYY	☐ M ☐ F	Child HCP#:

Information Source (and relation)

Contact Name (if different)	Contact Phone Number:

Birth Mother HCP#	Home Community/Health Centre

PAST PROBLEMS / RISK FACTORS / FAMILY HISTORY:

Age at Visit: _____ yrs _____mths

☐ TB Exposure

Current Family: ☐ Birth family ☐ Adopted ☐ Foster care
☐ Guardian care changed since 12 months old
Foster/Adopted Parents:_____

PARENT / GUARDIAN CONCERNS:

Height (cm)	Weight (g)	HC (cm)
%	%	%

NUTRITION (SINCE 12 MONTHS OLD)

Do You Currently Breastfeed? *(only check one)*
☐ Never breastfed
☐ No, discontinued at: _____ mths
☐ Breast milk in the past 7 days

Vitamin D Supplementation:
Do you have Vit. D drops at home? ☐ No ☐ Yes
If Yes: Are they given to baby? ☐ Never ☐ Sometimes ☐ Daily
Rickets Diagnosis: ☐ No ☐ Yes ☐ Unknown → Amt given: _____IU

How often does your child eat or drink:

Country Food (trad. meat, berries, etc.):	☐ Never	☐ < Once/week	☐ ≥ Once/week	☐ Daily or more
Sweetened drinks (crystals, pop, etc.):	☐ Never	☐ < Once/week	☐ ≥ Once/week	☐ Daily or more

Since your child was 12 months old:
Were there times when the food for you and your family just did not last and there was no money to buy enough food?
☐ Never ☐ Sometimes ☐ Often ☐ Don't know/Refused
Has your baby attended an early childhood care program? ☐ No ☐ Yes (specify): _____

DENTAL

Teeth brushing frequency: ☐ < Daily ☐ Daily ☐ > Daily
Tooth extractions: ☐ No ☐ Yes
Oral assessment: ☐ Healthy ☐ Unhealthy
Tooth decay (including white spots): ☐ No ☐ Yes

ENVIRONMENT

Maternal Smoking: ☐ No ☐ Yes → Amount (cig/day): _____
Location of smoking: ☐ Inside ☐ Outside
People smoking inside the house: _____
People in house: _____ # Bedrooms in house: _____

Substance use in household: ☐ No ☐ Yes ☐ Don't Know/Refused
Do you have any concerns regarding your child's safety? ☐No ☐ Yes
Nurse suspects abuse: ☐ No ☐ Yes ☐ Unsure
Social services involved: ☐ No ☐ Yes ☐ Unknown

PHYSICAL EXAMINATION / MEDICAL HISTORY

N = **N**ormal
A = **A**bnormal

	N	A
Blood pressure	☐	☐
Eyes (red reflex)/Visual acuity	☐	☐
Corneal light reflex	☐	☐
Cover-uncover test & inquiry	☐	☐
Hearing inquiry	☐	☐
Tonsil size / Teeth	☐	☐
Heart	☐	☐

Developmental Assessment: Parental concern about delay: ☐ No ☐ Yes
Tool used: _____
General development delay 'Impression' ☐ None ☐ Mild ☐ Moderate ☐ Severe
Speech/language delay 'Impression' ☐ None ☐ Mild ☐ Moderate ☐ Severe
Referred for support: ☐ P.T. ☐ O.T. ☐ Speech ☐ Other
Diagnosed developmental condition: _____

SINCE BIRTH: Had injury serious enough to seek medical attention: ☐ No ☐ Yes
If yes: Head injuries: ☐ No ☐ Yes → Injury severity: ☐ Mild ☐ Severe
Fractures: ☐ No ☐ Yes
Dental: ☐ No ☐ Yes Burns: ☐ No ☐ Yes

SINCE 12 MONTHS OLD: ☐ *Birth Defect Reporting Form completed*
Birth Defects detected: _____
Ear tube insertion: ☐ No ☐ Yes Chronic draining ears: ☐ No ☐ Yes
times Antibiotics taken for ear infections: _____
Reactive airway / Asthma: ☐ No ☐ Yes → If Yes: Age at onset: _____
Seizures: ☐ No ☐ Yes → If Yes: Meds required ☐ No ☐ Yes
w/ Fever ☐ No ☐ Yes ☐ Unknown
w/ Low blood sugar ☐ No ☐ Yes ☐ Unknown

Lung Infections: # Admissions: _____
Admission to: Type(s):
☐ Health centre ☐ Pneumonia
☐ Regional hospital ☐ Bronchiolitis
☐ Tertiary centre ☐ TB
☐ ICU ☐ Unknown ☐ Other

ANEMIA SCREENING

Hgb (fingerprick): _____
If needed, do venipunc
Hgb (venipunc): ☐ Done ☐ Not done

Lab Results: *(if venipunc - fill in later)*
Hgb _____
MCV _____ Ferritin _____ CRP _____

SINCE 12 MONTHS OLD:
Iron prescribed: ☐ No ☐ Yes
Iron taken: ☐ No ☐ Yes ☐ Sometimes

ASSESSMENT
Include notes on abnormal findings

☐ Well infant ☐ Needs follow-up ☐ Needs referral

VACCINES UP-TO-DATE: ☐ No ☐ Yes ☐ Unknown *(follow Nunavut Immunization Guide)*

SIGNATURE:

DATE: DD MM YYYY

Blue Writing: Indicates Questions NOT to be answered by the parent/guardian

CONTINUED ON REVERSE

WHITE: CHILD'S CHART YELLOW: NUTAQQAVUT HEALTH INFORMATION SYSTEM (IQALUIT)

Figure A.1.4 Nunavut well-baby record, 2-3 years (24 months)

NUNAVUT WELL-BABY RECORD

EVIDENCE-BASED INFANT/CHILD HEALTH MAINTENANCE GUIDE:

4 – 5 YEARS OLD

Surname	Given Name

Date of Birth DD MM YYYY	☐ M ☐ F	Child HCP#:

Information Source (and relation)

Contact Name (if different)	Contact Phone Number:

Birth Mother HCP#	Home Community/Health Centre

PAST PROBLEMS / RISK FACTORS / FAMILY HISTORY:

Age at Visit: _____ yrs _____mths

☐ TB Exposure

Current Family: ☐ Birth family ☐ Adopted ☐ Foster care
☐ Guardian care changed since previous visit (2-3 years old)
Foster/Adopted Parents: _____

PARENT / GUARDIAN CONCERNS:

Height (cm)	Weight (g)	HC (cm)
%	%	%

NUTRITION (SINCE 2-3 YEARS OLD)

How often does your child eat or drink:
Country Food (trad. meat, berries, etc.):
☐ Never ☐ < Once/week ☐ ≥ Once/week ☐ Daily or more
Sweetened drinks (crystals, pop, etc.):
☐ Never ☐ < Once/week ☐ ≥ Once/week ☐ Daily or more

Vitamin D Supplementation:
Do you have Vit. D drops at home? ☐ No ☐ Yes
If Yes: Are they given to your child?
☐ Never ☐ Sometimes ☐ Daily → Amt given: _____IU
Rickets Diagnosis: ☐ No ☐ Yes ☐ Unknown

Since your child was 2-3 years old:
Were there times when the food for you and your family just did not last and there was no money to buy enough food?
☐ Never ☐ Sometimes ☐ Often ☐ Don't know/Refused
Has your baby attended an early childhood care program? ☐ No ☐ Yes (specify): _____

DENTAL

Teeth brushing frequency: ☐ < Daily ☐ Daily ☐ > Daily
Tooth extractions: ☐ No ☐ Yes
Oral assessment: ☐ Healthy ☐ Unhealthy
Tooth decay (including white spots): ☐ No ☐ Yes

ENVIRONMENT

Maternal Smoking: ☐ No ☐ Yes → Amount (cig/day): _____
Location of smoking: ☐ Inside ☐ Outside
People smoking inside the house: _____
People in house: _____ # Bedrooms in house: _____

Substance use in household: ☐ No ☐ Yes ☐ Don't Know/Refused
Do you have any concerns regarding your child's safety? ☐ No ☐ Yes
Nurse suspects abuse: ☐ No ☐ Yes ☐ Unsure
Social services involved: ☐ No ☐ Yes ☐ Unknown

PHYSICAL EXAMINATION / MEDICAL HISTORY (SINCE 2-3 YEARS OLD)

N = **N**ormal
A = **A**bnormal

	N	A
Blood pressure	☐	☐
Eyes (red reflex)/Visual acuity	☐	☐
Corneal light reflex	☐	☐
Cover-uncover test & inquiry	☐	☐
Hearing inquiry	☐	☐
Tonsil size / Teeth	☐	☐
Heart	☐	☐

Developmental Assessment: Parental concern about delay: ☐ No ☐ Yes
Tool used: _____
General development delay 'Impression' ☐ None ☐ Mild ☐ Moderate ☐ Severe
Speech/language delay 'Impression' ☐ None ☐ Mild ☐ Moderate ☐ Severe
Referred for support: ☐ P.T. ☐ O.T. ☐ Speech ☐ Other
Diagnosed developmental condition: _____

SINCE 2-3 YEARS OLD: Had injury serious enough to seek medical attention: ☐ No ☐ Yes
If yes: Head injuries: ☐ No ☐ Yes → Injury severity: ☐ Mild ☐ Severe
Fractures: ☐ No ☐ Yes
Dental: ☐ No ☐ Yes Burns: ☐ No ☐ Yes

SINCE 2-3 YEARS OLD: ☐ *Birth Defect Reporting Form completed*
Birth Defects detected: _____
Ear tube insertion: ☐ No ☐ Yes Chronic draining ears: ☐ No ☐ Yes
times Antibiotics taken for ear infections: _____
Reactive airway / Asthma: ☐ No ☐ Yes → If Yes: Age at onset: _____
Seizures: ☐ No ☐ Yes → If Yes: Meds required ☐ No ☐ Yes
w/ Fever ☐ No ☐ Yes ☐ Unknown
w/ Low blood sugar ☐ No ☐ Yes ☐ Unknown

Lung Infections: # Admissions: _____
Admission to: ☐ Health centre ☐ Regional hospital ☐ Tertiary centre ☐ ICU ☐ Unknown
Type(s): ☐ Pneumonia ☐ Bronchiolitis ☐ TB ☐ Other

ANEMIA SCREENING

Hgb (fingerprick): _____
If needed, do venipunc
Hgb (venipunc): ☐ Done ☐ Not done

Lab Results: *(if venipunc - fill in later)*
Hgb _____
MCV _____ Ferritin _____ CRP _____

SINCE 2-3 YEARS OLD:
Iron prescribed: ☐ No ☐ Yes
Iron taken: ☐ No ☐ Yes ☐ Sometimes

ASSESSMENT
Include notes on abnormal findings

☐ Well infant ☐ Needs follow-up ☐ Needs referral

SIGNATURE:

DATE: DD MM YYYY

VACCINES UP-TO-DATE: ☐ No ☐ Yes ☐ Unknown *(follow Nunavut Immunization Guide)*

Blue Writing: Indicates Questions NOT to be answered by the parent/guardian

CONTINUED ON REVERSE

WHITE: CHILD'S CHART YELLOW: NUTAQQAVUT HEALTH INFORMATION SYSTEM (IQALUIT)

Figure A.1.5 Nunavut well-baby record, 4-5 years (48 months)

Figure A.1.6. Chart Review Protocol

Understanding the Role of the CPT1A P479L Variant in Infant and Child Health Outcomes in Nunavut

Conduct Protocol

Charts Required:

- Charts for infants born between Jan 1, 2010 and Dec 31, 2013.

Records Reviewed in Charts:

- Prenatal record
- Labour and delivery summary
- Newborn record
- Well-Baby records
- RSV Vaccination records
- Laboratory reports (those included in infant chart)
- Chart notes

Privacy:

- Chart reviewers will be required to sign a confidentiality agreement and complete the Canadian Tri-Council (CIHR, NSERC, SSHRC) tutorial on privacy and ethical conduct.
- Only health records for births during the study time period will be reviewed.
- All data will be password protected and encrypted (converted to code that is not readable without the needed password).
- Upon completion of the chart review, records will be de-identified by removing direct identifiers (like day of birth).
- Data will be collected on Microsoft Bitlocker encrypted laptops and will be backed up and stored on the UVic Island Medical Program Unix secure server which requires password authentication for access. The server is located in a custom built secure enterprise data centre.

Chart Reviewers Needs (at each location):

- Desk/table, chair and power source.
- Internet access would be helpful but is not required.
- Organisation of travel and accommodations will be done by the chart reviewers – chart reviewers will be reimbursed for expenses through UBC.

Health Centre Consultations:

- An introductory letter or email will be sent to health centre administrators and personnel. The letter will summarise the project goals, objectives and review process.
- After distribution of the letter, the project manager Ms. Sorcha Collins will contact the health centre, answer questions about the project and finalise the review process and timelines for that centre. She will also ensure that the impact to centre routine and staff is minimised (i.e. whether chart reviewers would be able to pull charts so as to not increase workload for health centre personnel). Additional information or meetings with project team members will be available for those requiring further details or in-depth information.

Pulling Charts:

- In the initial days of the review, 10 charts will be pulled daily. The team will work with the health centre regarding whether the chart reviewers or health centre staff will pull charts. In previous chart reviews, 15-20 charts, on average, were reviewed daily by each reviewer in an 8hr work day. After the initial days of the review, the number of charts to be pulled daily will be reviewed.

Shelving Charts:

- The team will work with the health centre to determine how charts will be refiled. In previous chart reviews, health centre staff members have refiled charts to ensure they are correctly filed.
- This may require the allocation of study funds to reimburse the centre for wages while refiling, which can be determined during the consultation with the health centre prior to initiating the chart review or once the project has been initiated.

A.2 SUB-APPENDIX

Table A.2.1 Pairwise correlation for NH variables for Kivalliq Inuit newborns born in Winnipeg Manitoba, 2010-2013 (n=616)

	NH	p.P479L Hmz	p.P479L Het	Mat DM	Mat Htn	Precla-mpsia	Clinical Risk	Male	GA	PTB	BW	SGA	LGA	Term-NRF	BY: 2010	BY: 2011	BY: 2012	BY: 2013
p.P479L Hmz	0.041	1.00																
p	0.326																	
p.P479L Het	-0.019	**-0.879**	1.00															
p	0.644	<0.001																
Mat DM	**0.089**	0.064	-0.073	1.00														
p	0.028	0.129	0.084															
Mat Htn	**0.186**	-0.066	0.047	**0.094**	1.00													
p	<0.001	0.118	0.268	0.019														
Preeclampsia	0.016	0.046	-0.048	0.028	-0.044	1.00												
p	0.693	0.269	0.254	0.493	0.273													
Clinical Risk	-0.041	0.006	-0.018	-0.020	0.039	**0.093**	1.00											
p	0.313	0.892	0.674	0.621	0.336	0.022												
Male	**0.087**	0.013	-0.012	0.018	0.039	-0.003	0.054	1.00										
p	0.032	0.756	0.785	0.660	0.337	0.941	0.178											
GA	-0.049	**-0.139**	**0.101**	0.026	-0.031	-0.012	**-0.097**	0.012	1.00									
p	0.226	0.001	0.016	0.524	0.441	0.770	0.016	0.761										
PTB	0.034	0.054	0.031	0.053	0.020	0.004	**0.116**	-0.016	**-0.649**	1.00								
p	0.388	0.199	0.457	0.192	0.630	0.928	0.004	0.685	<0.001									
Birth weight	-0.061	**-0.170**	**0.161**	0.061	-0.059	0.001	-0.068	**0.130**	**0.559**	**-0.422**	1.00							
p	0.129	0.000	0.000	0.133	0.142	0.987	0.092	0.001	<0.001	<0.001								
SGA	0.018	0.020	-0.006	-0.041	0.059	-0.046	0.053	-0.038	0.002	0.036	**-0.403**	1.00						
p	0.659	0.640	0.887	0.306	0.147	0.251	0.185	0.343	0.963	0.380	0.000							
LGA	-0.057	**-0.102**	**0.115**	0.003	-0.001	-0.039	-0.004	-0.011	**0.096**	**-0.084**	**0.576**	**-0.093**	1.00					
p	0.159	0.015	0.006	0.935	0.987	0.336	0.924	0.786	0.016	0.038	0.000	0.021						
Term-NRF	-0.058	-0.007	-0.018	**-0.203**	**-0.301**	**-0.228**	**-0.412**	-0.007	**0.249**	**-0.401**	0.029	**-0.314**	**-0.456**	1.00				
p	0.152	0.861	0.673	<0.001	<0.001	<0.001	<0.001	0.865	<0.001	<0.001	0.470	<0.001	<0.001					
BY: 2010	**0.151**	-0.045	0.032	0.012	**0.111**	0.013	0.007	-0.032	-0.010	0.014	-0.060	0.014	-0.062	-0.021	1.00			
p	<0.001	0.288	0.448	0.776	0.006	0.749	0.863	0.426	0.809	0.735	0.140	0.735	0.125	0.610				
BY: 2011	-0.050	-0.064	0.060	0.013	0.009	-0.011	0.013	0.030	-0.006	-0.050	**0.080**	-0.050	0.053	-0.014	**-0.330**	1.00		
p	0.217	0.128	0.152	0.753	0.825	0.780	0.749	0.460	0.880	0.216	0.048	0.216	0.188	0.738	<0.001			
BY: 2012	-0.050	0.034	-0.035	0.007	-0.047	0.043	0.037	0.015	0.075	0.032	0.018	0.032	0.006	0.052	**-0.343**	**-0.400**	1.00	
p	0.213	0.419	0.407	0.868	0.248	0.290	0.363	0.720	0.065	0.429	0.661	0.429	0.881	0.199	<0.001	<0.001		
BY: 2013	-0.043	0.077	-0.059	-0.033	-0.071	-0.049	-0.063	-0.016	-0.067	0.005	-0.047	0.005	-0.002	-0.022	**-0.273**	**-0.318**	**-0.330**	1.00
p	0.285	0.068	0.163	0.409	0.077	0.228	0.121	0.686	0.097	0.897	0.242	0.897	0.959	0.582	<0.001	<0.001	<0.001	

NH: neonatal hypoglycemia, Hmz (LL): homozygous for carnitine palmitoyltransferase 1A p.P479L variant, Het (PL): heterozygous for the carnitine palmitoyltransferase 1A p.P479L variant Mat DM: maternal diabetes, pre-existing or gestational, Mat hypertension without preeclampsia. Clinical risks: asphyxia, infection, transient tachypnea of the newborn (TTN), chorioamnionitis and major congenital anomalies. GA: gestational age, PTB: Preterm birth (<37 weeks gestation), BW: birth weight (g), SGA: small for gestational age (<10^{th} percentile), LGA: large for gestational age (>90^{th} percentile), Term-NRF newborns: term newborns (≥37weeks gestation) with no risk factors for neonatal hypoglycemia; excludes preterm birth, small for gestational age, large for gestational age, macrosomia, maternal pre-existing or gestational diabetes, maternal hypertension, maternal preeclampsia, other clinical risks for hypoglycemia, BY: Birth year.

A.3 SUB-APPENDIX

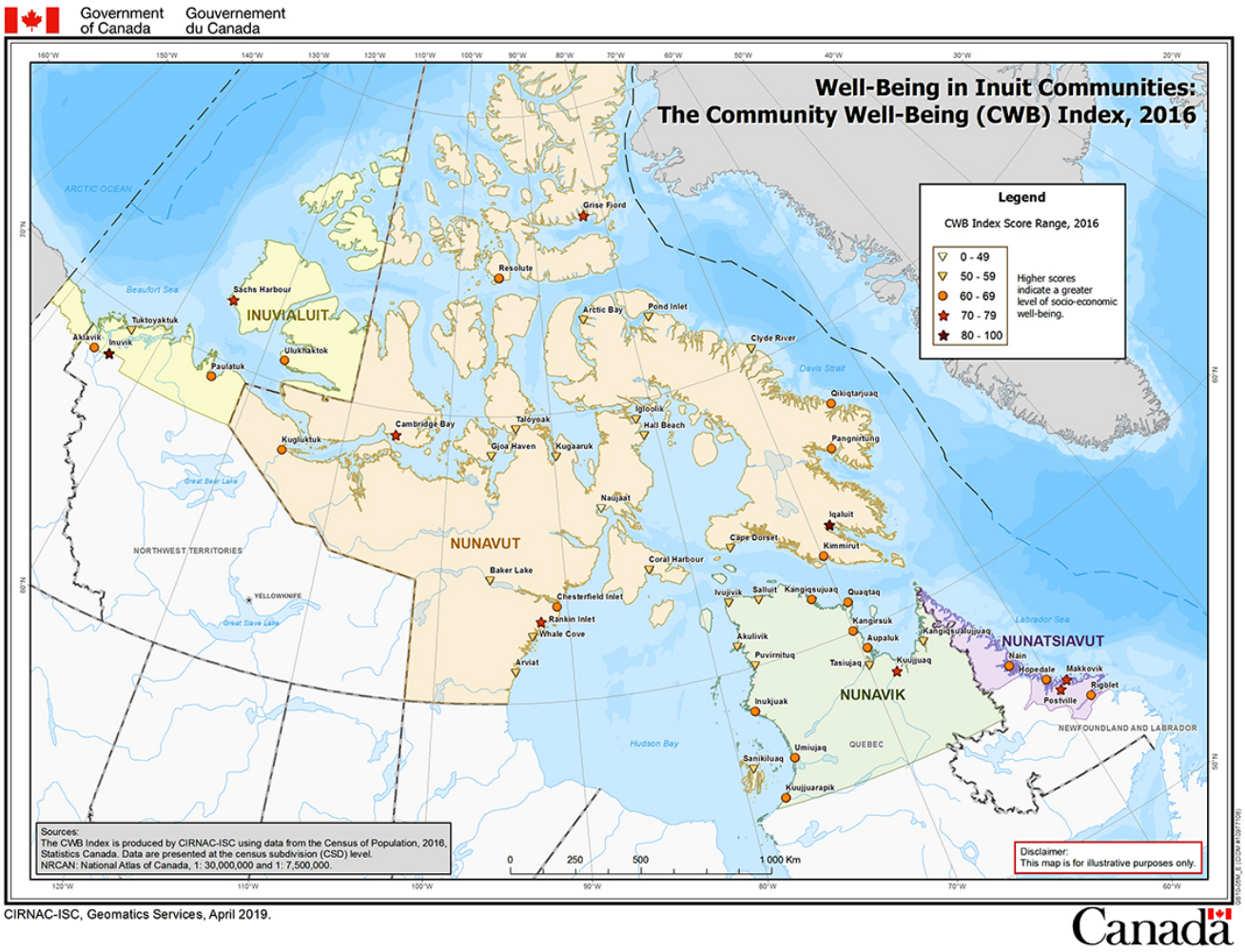

Figure A.3.1 Community well-being index of Inuit communities.
Reproduced from Community well-being index. Report on trends in Inuit communities, 1981 to 2016 [222].

Table A.3.1 Univariable and multivariable logistic regression models for admission for lower respiratory tract infection (LRTI) in Inuit children from Nunavut (2010-2013).

	Early childhood (0-5yrs)						Infants (<1yr)					
	Univariable Analysis		Model 1 (n=2225)		Model 2 (n=1697)		Univariable Analysis		Model 1 (n=2225)		Model 2 (n=1697)	
	OR (95%CI)	p	aOR (95%CI)	p	aOR (95%CI)	p	OR (95%CI)	p	aOR (95%CI)	p	aOR (95%CI)	p
CPT1A p.P479L												
Hmz (LL)	3.47 (2.00-6.01)	<0.001	3.19 (1.82-5.60)	<0.001	2.88 (1.46-5.64)	0.002	4.15 (2.08-8.25)	<0.001	3.28 (1.63-6.58)	0.001	2.79 (1.29-6.03)	0.009
Het (PL)	1.66 (0.93-2.95)	0.088	1.62 (0.90-2.90)	0.107	1.63 (0.81-3.29)	0.169	1.82 (0.89-3.76)	0.103	1.64 (0.79-3.39)	0.182	1.54 (0.69-3.44)	0.291
CWB	0.80 (0.73-0.89)	<0.001	0.66 (0.56-0.78)	<0.001	0.72 (0.59-0.87)	0.001	0.69 (0.61-0.78)	<0.001	0.71 (0.59-0.85)	<0.001	0.77 (0.63-0.95)	0.015
Iqaluit	0.93 (0.69-1.25)	0.629	3.37 (2.00-5.66)	<0.001	2.70 (1.44-5.08)	0.002	0.49 (0.33-0.73)	<0.001	1.48 (0.81-2.74)	0.206	1.46 (0.70-3.04)	0.307
Male	1.12 (0.93-1.35)	0.236			1.11 (0.88-1.38)	0.376	1.22 (0.99-1.51)	0.058			1.24 (0.97-1.59)	0.083
Preterm birth	1.91 (1.47-2.50)	<0.001			1.75 (1.27-2.42)	0.001	2.12 (1.60-2.81)	<0.001			1.81 (1.28-2.54)	0.001
CHD	2.38 (1.41-4.03)	0.001			2.52 (1.38-4.61)	0.003	2.89 (1.70-4.93)	<0.001			2.95 (1.60-5.44)	0.001
Other CAs	2.55 (1.50-4.35)	0.001			2.75 (1.46-5.18)	0.002	2.08 (1.18-3.65)	0.011			2.31 (1.21-4.41)	0.011
BF ≥6mths	0.64 (0.52-0.78)	<0.001			0.70 (0.55-0.88)	0.002	0.65 (0.51-0.82)	<0.001			0.70 (0.54-0.91)	0.006
Mat. smoking	1.47 (1.07-2.02)	0.018			1.16 (0.82-1.65)	0.400	1.40 (0.98-2.00)	0.061			1.05 (0.72-1.54)	0.800
Food insecure	1.45 (1.18-1.79)	0.001			1.38 (1.10-1.73)	0.005	1.36 (1.08-1.71)	0.010			1.25 (0.98-1.60)	0.077

OR: odds ratio, CI: confidence interval, aOR: adjusted odds ratio, CPT1A: carnitine palmitoyltransferase 1A, Hmz (LL): homozygous for CPT1A p.P479L variant, Het (PL): heterozygous for the CPT1A p.P479L variant, CWB: community well-being index, Iqaluit: residence in Iqaluit, Preterm birth: <37weeks gestation, CHD: presence of congenital heart defect, Other CAs: presence of other major congenital anomalies, BF ≥6mths: breastfeeding for 6 months of longer, Mat. smoke: postnatal maternal smoking.

Table A.3.2 Univariable and complete case multivariable logistic regression models for admission for respiratory syncytial virus (RSV) in Inuit children from Nunavut (2010-2013).

	Early childhood (0-5yrs)						Infants (<1yr)					
	Univariable Analysis		Model 1 (n=2225)		Model 2 (n=1697)		Univariable Analysis		Model 1 (n=2225)		Model 2 (n=1697)	
	OR (95%CI)	p	aOR (95%CI)	p	aOR (95%CI)	p	OR (95%CI)	p	aOR (95%CI)	p	aOR (95%CI)	p
CPT1A p.P479L												
Hmz (LL)	4.13 (1.30-13.15)	0.016	4.17 (1.29-13.47)	0.017	3.04 (0.92-10.07)	0.068	3.33 (1.04-10.64)	0.042	2.89 (0.89-9.36)	0.077	2.02 (0.61-6.71)	0.249
Het (PL)	3.02 (0.92-9.92)	0.069	3.07 (0.93-10.13)	0.066	2.61 (0.77-8.82)	0.122	2.36 (0.71-7.85)	0.161	2.23 (0.67-7.43)	0.193	1.79 (0.52-6.11)	0.355
CWB	0.92 (0.79-1.08)	0.317	0.78 (0.59-1.02)	0.066	0.81 (0.60-1.09)	0.172	0.80 (0.67-0.97)	0.022	0.75 (0.56-1.00)	0.051	0.80 (0.58-1.10)	0.174
Iqaluit	1.16 (0.73-1.83)	0.532	2.61 (1.15-5.91)	0.022	3.11 (1.24-7.79)	0.015	0.74 (0.41-1.33)	0.317	1.78 (0.70-4.55)	0.230	1.90 (0.65-5.57)	0.241
Male	0.90 (0.66-1.21)	0.476			0.91 (0.65-1.29)	0.596	0.92 (0.66-1.28)	0.611			0.96 (0.66-1.41)	0.838
Preterm birth	1.23 (0.79-1.90)	0.356			1.16 (0.69-1.94)	0.570	0.99 (0.60-1.66)	0.981			0.95 (0.52-1.74)	0.879
CHD	1.31 (0.55-3.08)	0.543			1.50 (0.62-3.62)	0.372	1.33 (0.52-3.37)	0.554			1.56 (0.60-4.07)	0.359
Other CAs	1.36 (0.57-3.21)	0.485			1.81 (0.74-4.41)	0.193	1.07 (0.38-3.01)	0.892			1.43 (0.50-4.12)	0.505
BF ≥6mths	0.93 (0.67-1.29)	0.661			0.92 (0.64-1.31)	0.636	0.93 (0.65-1.33)	0.674			0.98 (0.66-1.45)	0.912
Mat. smoking	1.17 (0.71-1.93)	0.531			1.06 (0.62-1.79)	0.843	1.29 (0.73-2.29)	0.381			1.15 (0.62-2.11)	0.658
Food insecure	1.26 (0.90-1.75)	0.172			1.25 (0.88-1.78)	0.214	1.28 (0.89-1.85)	0.181			1.24 (0.84-1.82)	0.284

OR: odds ratio, CI: confidence interval, aOR: adjusted odds ratio, CPT1A: carnitine palmitoyltransferase 1A, Hmz (LL): homozygous for CPT1A p.P479L variant, Het (PL): heterozygous for the CPT1A p.P479L variant, CWB: community well-being index, Iqaluit: residence in Iqaluit, Preterm birth: <37weeks gestation, CHD: presence of congenital heart defect, Other CAs: presence of other major congenital anomalies, BF ≥6mths: breastfeeding for 6 months of longer, Mat. smoke: postnatal maternal smoking.

Table A.3.3 Univariable and complete case multivariable logistic regression models for episodes of otitis media in Inuit children from Nunavut (2010-2013).

	Early childhood (0-5yr)						Infants (<1yr)					
	Univariable Analysis		Model 1 (n=2225)		Model 2 (n=1697)		Univariable Analysis		Model 1 (n=2225)		Model 2 (n=1697)	
	OR (95%CI)	p	aOR (95%CI)	p	aOR (95%CI)	p	OR (95%CI)	p	aOR (95%CI)	p	aOR (95%CI)	p
CPT1A p.P479L												
Hmz (LL)	3.12 (2.05-4.73)	<0.001	1.95 (1.25-3.06)	0.004	1.83 (1.05-3.21)	0.034	2.83 (1.96-4.09)	<0.001	1.83 (1.24-2.70)	0.003	1.87 (1.18-2.96)	0.008
Het (PL)	1.97 (1.26-3.07)	0.003	1.64 (1.03-2.61)	0.036	1.67 (0.94-2.99)	0.081	1.70 (1.15-2.51)	0.008	1.41 (0.94-2.12)	0.096	1.53 (0.95-2.47)	0.084
CWB	0.58 (0.52-0.65)	<0.001	0.77 (0.62-0.95)	0.014	0.74 (0.58-0.95)	0.017	0.58 (0.53-0.64)	<0.001	0.68 (0.59-0.79)	<0.001	0.67 (0.57-0.79)	<0.001
Iqaluit	0.22 (0.17-0.30)	<0.001	0.47 (0.27-0.82)	0.008	0.44 (0.22-0.86)	0.017	0.24 (0.18-0.31)	<0.001	0.67 (0.43-1.04)	0.073	0.65 (0.38-1.10)	0.108
Male	1.00 (0.79-1.27)	0.997			0.97 (0.72-1.31)	0.854	1.12 (0.94-1.33)	0.194			1.09 (0.88-1.34)	0.435
Preterm birth	0.83 (0.58-1.18)	0.289			0.65 (0.42-0.99)	0.044	0.82 (0.63-1.07)	0.145			0.68 (0.50-0.94)	0.018
BF ≥6mths	0.99 (0.76-1.29)	0.940			0.99 (0.73-1.34)	0.954	0.97 (0.81-1.17)	0.768			1.00 (0.81-1.24)	0.992
Mat. smoking	1.43 (0.99-2.07)	0.055			1.08 (0.71-1.63)	0.729	1.23 (0.94-1.62)	0.138			1.01 (0.74-1.37)	0.948
Food insecure	1.19 (0.90-1.59)	0.227			0.89 (0.65-1.23)	0.487	1.06 (0.87-1.29)	0.550			0.85 (0.68-1.05)	0.129

OR: odds ratio, CI: confidence interval, aOR: adjusted odds ratio, CPT1A: carnitine palmitoyltransferase 1A, Hmz (LL): homozygous for CPT1A p.P479L variant, Het (PL): heterozygous for the CPT1A p.P479L variant, CWB: community well-being index, Iqaluit: residence in Iqaluit, Preterm birth: <37weeks gestation, BF ≥6mths: breastfeeding for 6 months of longer, Mat. smoke: postnatal maternal smoking.

Table A.3.4 Univariable and complete case multivariable logistic regression models for episodes of gastroenteritis in Inuit children from Nunavut (2010-2013).

	Early childhood (0-5yr)						Infants (<1yr)					
	Univariable Analysis		Model 1 (n=2225)		Model 2 (n=1697)		Univariable Analysis		Model 1 (n=2225)		Model 2 (n=1697)	
	OR (95%CI)	p	aOR (95%CI)	p	aOR (95%CI)	p	OR (95%CI)	p	aOR (95%CI)	p	aOR (95%CI)	p
CPT1A p.P479L												
Hmz (LL)	1.91 (1.31-2.78)	0.001	1.62 (1.10-2.38)	0.015	1.74 (1.09-2.77)	0.020	2.58 (1.57-4.26)	<0.001	2.00 (1.20-3.34)	0.008	2.32 (1.23-4.39)	0.010
Het (PL)	1.30 (0.87-1.93)	0.197	1.21 (0.81-1.81)	0.344	1.32 (0.81-2.13)	0.264	1.79 (1.06-3.02)	0.030	1.61 (0.95-2.73)	0.078	2.01 (1.04-3.87)	0.037
CWB	0.80 (0.73-0.87)	<0.001	0.71 (0.62-0.82)	<0.001	0.70 (0.59-0.82)	<0.001	0.71 (0.64-0.79)	<0.001	0.60 (0.51-0.70)	<0.001	0.60 (0.50-0.72)	<0.001
Iqaluit	0.75 (0.58-0.98)	0.037	1.93 (1.26-2.97)	0.003	1.23 (0.73-2.07)	0.444	0.66 (0.48-0.90)	0.009	2.67 (1.59-4.48)	<0.001	1.93 (1.02-3.65)	0.044
Male	1.20 (1.01-1.41)	0.036			1.17 (0.96-1.42)	0.117	1.28 (1.07-1.54)	0.008			1.27 (1.02-1.57)	0.029
Preterm birth	0.85 (0.66-1.10)	0.211			0.85 (0.63-1.16)	0.310	0.99 (0.74-1.31)	0.927			0.96 (0.69-1.34)	0.825
BF ≥6mths	0.84 (0.70-1.01)	0.059			0.85 (0.70-1.04)	0.107	0.60 (0.49-0.74)	<0.001			0.59 (0.47-0.74)	<0.001
Mat. smoking	1.06 (0.81-1.38)	0.663			0.87 (0.65-1.16)	0.338	1.19 (0.89-1.61)	0.244			0.95 (0.68-1.31)	0.748
Food insecure	1.16 (0.96-1.40)	0.119			1.03 (0.85-1.26)	0.748	1.16 (0.95-1.42)	0.153			1.07 (0.86-1.33)	0.544

OR: odds ratio, CI: confidence interval, aOR: adjusted odds ratio, CPT1A: carnitine palmitoyltransferase 1A, Hmz (LL): homozygous for CPT1A p.P479L variant, Het (PL): heterozygous for the CPT1A p.P479L variant, CWB: community well-being index, Iqaluit: residence in Iqaluit, Preterm birth: <37weeks gestation, BF ≥6mths: breastfeeding for 6 months of longer, Mat. smoke: postnatal maternal smoking.

Table A.3.5 Univariable and complete case multivariable logistic regression models for dental interventions in Inuit children (0-5yrs) from Nunavut (2010-2013).

	Univariable Analysis		**Model 1 (n=2225)**		**Model 2 (n=1697)**	
	OR (95%CI)	**p**	**aOR (95%CI)**	**p**	**aOR (95%CI)**	**p**
CPT1A p.P479L						
Hmz (LL)	3.14 (1.98-5.00)	<0.001	2.23 (1.38-3.58)	0.001	2.11 (1.22-3.66)	0.008
Het (PL)	2.37 (1.46-3.84)	<0.001	2.06 (1.26-3.36)	0.004	1.88 (1.07-3.32)	0.029
CWB	0.65 (0.59-0.72)	<0.001	0.60 (0.52-0.70)	<0.001	0.51 (0.43-0.61)	<0.001
Iqaluit	0.44 (0.32-0.60)	<0.001	1.70 (1.05-2.74)	0.031	2.38 (1.33-4.28)	0.004
Male	1.03 (0.87-1.22)	0.739	0.27 (0.17-0.43)	<0.001	1.04 (0.85-1.27)	0.712
Preterm birth	1.09 (0.84-1.42)	0.521			1.05 (0.76-1.43)	0.779
BF ≥6mths	0.83 (0.69-1.00)	0.053			0.87 (0.71-1.07)	0.186
Mat. smoking	1.21 (0.92-1.60)	0.175			0.98 (0.73-1.33)	0.922
Food insecure	1.05 (0.86-1.27)	0.636			0.90 (0.73-1.10)	0.303

OR: odds ratio, CI: confidence interval, aOR: adjusted odds ratio, CPT1A: carnitine palmitoyltransferase 1A, Hmz (LL): homozygous for CPT1A p.P479L variant, Het (PL): heterozygous for the CPT1A p.P479L variant, CWB: community well-being index, Iqaluit: residence in Iqaluit, Preterm birth: <37weeks gestation, BF ≥6mths: breastfeeding for 6 months of longer, Mat. smoke: postnatal maternal smoking.

Table A.3.6 Multivariable logistic regression model 2 results using multiple imputation data (20 imputations, n=2225)

	LRTI admit				RSV admit			
	Early Childhood (0-5yrs)		Infancy (<1yr)		Early Childhood (0-5yrs)		Infancy (<1yr)	
	aOR (95%CI)	p	aOR (95%CI)	p	aOR (95%CI)	p	aOR (95%CI)	p
CPT1A p.P479L								
Hmz (LL)	3.11 (1.75-5.52)	<0.001	3.26 (1.60-6.64)	0.001	4.12 (1.27-13.41)	0.019	2.81 (0.86-9.18)	0.087
Het (PL)	1.64 (0.91-2.98)	0.102	1.69 (0.81-3.54)	0.161	3.11 (0.94-10.32)	0.064	2.23 (0.66-7.47)	0.194
CWB	0.68 (0.57-0.80)	<0.001	0.73 (0.60-0.87)	0.001	0.78 (0.60-1.03)	0.077	0.75 (0.56-1.01)	0.057
Iqaluit	3.57 (2.10-6.07)	<0.001	1.52 (0.81-2.83)	0.190	2.67 (1.17-6.08)	0.020	1.82 (0.71-4.70)	0.212
Male	1.07 (0.88-1.30)	0.483	1.17 (0.94-1.45)	0.152	0.88 (0.64-1.19)	0.395	0.90 (0.65-1.26)	0.546
Preterm birth	1.81 (1.37-2.38)	<0.001	1.97 (1.47-2.64)	<0.001	1.24 (0.79-1.92)	0.347	0.98 (0.59-1.64)	0.937
CHD	2.28 (1.31-3.94)	0.003	2.69 (1.54-4.72)	0.001	1.28 (0.54-3.04)	0.581	1.28 (0.50-3.29)	0.604
Other CAs	2.42 (1.35-4.36)	0.003	2.06 (1.11-3.82)	0.021	1.27 (0.49-3.27)	0.618	1.24 (0.44-3.50)	0.691
BF ≥6mths	1.14 (0.81-1.61)	0.439	1.07 (0.74-1.53)	0.730	0.97 (0.60-1.57)	0.887	1.04 (0.60-1.80)	0.885
Mat. smoking	0.67 (0.54-0.83)	<0.001	0.69 (0.54-0.87)	0.002	0.94 (0.68-1.31)	0.723	0.94 (0.65-1.35)	0.740
Food insecure	1.34 (1.05-1.69)	0.017	1.21 (0.94-1.56)	0.134	1.20 (0.85-1.70)	0.299	1.18 (0.80-1.73)	0.395

	Otitis Media				Gastroenteritis				Dental	
	Early Childhood (<5yr)		Infancy (<1yr)		Early Childhood (0-5yrs)		Infancy (<1yr)		Early Childhood (0-5yrs)	
	aOR (95%CI)	p	aOR (95%CI)	p	aOR (95%CI)	p	aOR (95%CI)	p	aOR (95%CI)	p
CPT1A p.P479L										
Hmz (LL)	1.96 (1.24-3.10)	0.004	1.90 (1.28-2.82)	0.002	1.65 (1.11-2.44)	0.013	2.00 (1.19-3.36)	0.009	2.27 (1.41-3.67)	0.001
Het (PL)	1.64 (1.02-2.62)	0.040	1.44 (0.95-2.17)	0.082	1.24 (0.83-1.86)	0.302	1.62 (0.95-2.77)	0.075	2.09 (1.27-3.41)	0.003
CWB	0.76 (0.61-0.94)	0.012	0.67 (0.58-0.78)	<0.001	0.71 (0.62-0.82)	<0.001	0.60 (0.51-0.71)	<0.001	0.60 (0.52-0.70)	<0.001
Iqaluit	0.47 (0.27-0.82)	0.008	0.66 (0.43-1.03)	0.070	1.91 (1.24-2.93)	0.003	2.57 (1.53-4.34)	<0.001	1.65 (1.02-2.67)	0.041
Male	0.98 (0.76-1.25)	0.855	1.11 (0.93-1.33)	0.237	1.19 (1.00-1.40)	0.048	1.25 (1.04-1.51)	0.020	1.00 (0.84-1.19)	0.996
Preterm birth	0.76 (0.52-1.09)	0.137	0.75 (0.57-0.99)	0.042	0.79 (0.61-1.02)	0.076	0.86 (0.64-1.16)	0.320	1.03 (0.79-1.35)	0.821
BF ≥6mths	1.09 (0.73-1.62)	0.689	0.97 (0.73-1.29)	0.814	0.85 (0.64-1.13)	0.262	0.91 (0.66-1.24)	0.544	0.98 (0.74-1.31)	0.909
Mat. smoking	0.99 (0.75-1.31)	0.934	1.00 (0.82-1.21)	0.972	0.87 (0.72-1.04)	0.121	0.63 (0.51-0.77)	<0.001	0.86 (0.71-1.04)	0.127
Food insecure	0.91 (0.67-1.24)	0.551	0.84 (0.68-1.04)	0.118	1.04 (0.85-1.27)	0.700	1.04 (0.84-1.28)	0.724	0.89 (0.72-1.10)	0.293

OR: odds ratio, CI: confidence interval, aOR: adjusted odds ratio, CPT1A: carnitine palmitoyltransferase 1A, Hmz (LL): homozygous for CPT1A p.P479L variant, Het (PL): heterozygous for the CPT1A p.P479L variant, LRTI: lower respiratory tract infection, RSV: respiratory syncytial virus, Preterm birth: <37weeks gestation, CHD: presence of congenital heart defect, Other CAs: presence of other major congenital anomalies, BF ≥6mths: breastfeeding for 6 months of longer, Mat. smoke: postnatal maternal smoking