Université de Montréal

# Neonatal intraventricular hemorrhage and hospitalization in childhood

*Par*

Amarpreet Kaur

Département de médecine sociale et préventive

École de santé publique

Mémoire présenté en vue de l'obtention du grade de

Maîtrise ès sciences en Épidémiologie

Août 2019

Université de Montréal

Unité académique : Département de médicine sociale et présentative, École de santé publique

---

*Ce mémoire intitulé*

**Neonatal intraventricular hemorrhage and hospitalization in childhood**

*Présenté par*

**Amarpreet Kaur**

*A été évalué par un jury composé des personnes suivantes*

**Dre Lise Gauvin**
Président-rapporteur

**Dre Nathalie Auger**
Directeur de recherche

**Dre Marie-Claude Rousseau**
Membre du jury

# Résumé

**Contexte:** L'hémorragie intraventriculaire néonatale est associée à des séquelles neuro-développementales, mais le risque à long terme d'autres issues est inconnu. L'association entre l'hémorragie intraventriculaire néonatale et le risque de morbidité durant l'enfance a été évaluée.

**Méthodes:** Une cohorte longitudinale de 794,384 bébés nés entre 2006 et 2016 au Québec, Canada a été analysé. Les nouveau-nés ont été suivis jusqu'à une période de 12 ans après leur naissance, pour identifier les hospitalisations subséquentes. Dans les modèles de régression de Cox, ajustés pour les caractéristiques maternelles et néonatales, les « hazard ratios » et intervalles de confiance (IC) à 95% ont été estimés pour l'association entre l'hémorragie intraventriculaire avec l'hospitalisation ultérieure.

**Résultats:** Au total, 1,322 nourrissons (0,2%) ont développé une hémorragie intraventriculaire de grade I à IV. L'incidence de l'hospitalisation était plus élevée chez les bébés présentant une hémorragie intraventriculaire que chez les bébés sans hémorragie (23,8 vs 5,7 par 100 personnes-années). Comparés aux bébés sans hémorragie, les bébés affectés avaient un risque d'hospitalisation 1,56 fois plus élevé (IC à 95% 1,43-1,70). Le risque était 2,81 fois plus élevé pour les grades III/IV (IC à 95% 2,23 à 3,53) comparés à ceux nés sans hémorragie. Les hémorragies intraventriculaires pré-terme était associée à 1,82 fois le risque (IC 95% 1,66-2,00) comparés aux bébés nés termes sans hémorragie. Les hémorragies intraventriculaires à terme étaient associées à 3,19 fois le risque d'hospitalisation (IC 95% 2,55-4,00), comparativement à ceux nés termes sans hémorragie. Les raisons principales des hospitalisations comprenaient les maladies du système nerveux central, ophtalmologiques, musculo-squelettiques et cardiovasculaires.

**Conclusion:** L'hémorragie intraventriculaire, notamment de grades sévères et parmi les bébés à terme, est un déterminant important du futur risque d'hospitalisation durant l'enfance.

**Mots-clés**: Hémorragie cérébrale; Hospitalisation; Effet à long terme; Morbidité; Bébé prématuré

# Abstract

**Background**: Neonatal intraventricular hemorrhage is associated with neurodevelopmental sequelae, but the long-term risk of other outcomes is unknown. The association between neonatal intraventricular hemorrhage and the risk of childhood morbidity was assessed.

**Methods**: A longitudinal cohort of 794,384 infants born between 2006 and 2016 in Quebec, Canada was analyzed. Infants were tracked over time to identify later hospitalizations with follow-up extending up to 12 years after birth. In Cox regression models adjusted for maternal and infant characteristics, the hazard ratios and 95% confidence intervals (CI) were estimated for the association of intraventricular hemorrhage with future hospitalization.

**Results:** A total of 1,322 (0.2%) infants developed grade I to IV intraventricular hemorrhage. The incidence of childhood hospitalization was higher in infants with intraventricular hemorrhage than in infants without hemorrhage (23.8 vs. 5.7 per 100 person-years). Compared with no hemorrhage, infants with intraventricular hemorrhage had 1.56 times the risk of hospitalization (95% CI 1.43-1.70). The risk was 2.81 times higher for grade III/IV hemorrhage (95% CI 2.23-3.53) compared to those born without hemorrhage. Preterm intraventricular hemorrhage was associated with 1.82 times the risk (95% CI 1.66-2.00) compared to term infants born without hemorrhage. Intraventricular hemorrhage at term was associated with 3.19 times the risk of hospitalization (95% CI 2.55-4.00) compared to those born term without hemorrhaging. Primary reasons for hospitalizations included central nervous system, ophthalmologic, musculoskeletal, and cardiovascular disorders.

**Conclusion:** Intraventricular hemorrhage, especially of higher grades and in term neonates, is an important determinant of the future risk of child hospitalization.

**Keywords**: Brain hemorrhage; Hospitalization; Long-term effect; Morbidity; Preterm infant

# Table of contents

Résumé ..... 5

Abstract ..... 7

Table of contents ..... 9

List of tables ..... 13

List of figures ..... 15

List of abbreviations ..... 17

Acknowledgments ..... 21

Chapter 1 ..... 23

1. Introduction ..... 23

Chapter 2 ..... 25

2. Literature review ..... 25

2.1 Definition and descriptive epidemiology ..... 25

2.1.1 Pathophysiology and risk factors of intraventricular hemorrhage ..... 25

2.1.2 Severity of intraventricular hemorrhage ..... 27

2.1.3 Timing of intraventricular hemorrhage ..... 28

2.1.4 Public health implications ..... 30

2.2 Neonatal characteristics ..... 31

2.2.1 Gestational age ..... 31

2.2.2 Birthweight ..... 31

2.2.3 Infant sex ..... 31

2.2.4 Neonatal comorbidities ..... 32

2.3 Maternal characteristics ..... 34

2.3.1 Age ..... 34

2.3.2 Socioeconomic status ..... 34
2.3.3 Rurality ..... 34
2.3.4 Pregnancy complications ..... 35
2.4 Current knowledge of intraventricular hemorrhage outcomes ..... 36
2.4.1 Long-term neurodevelopmental outcomes ..... 36
2.4.2 Long-term morbidity ..... 38
2.4.3 Mortality ..... 39
2.5 Summary of literature review ..... 40
2.6 Research objectives ..... 41
Chapter 3 ..... 43
3. Conceptual framework ..... 43
Chapter 4 ..... 45
4. Methods ..... 45
4.1 Context and study design: Analysis of secondary data ..... 45
4.2 Population and exclusion criteria ..... 45
4.3 Definition of exposure ..... 46
4.4 Definition of outcomes ..... 48
4.5 Definition of covariates ..... 51
4.6 Data analysis ..... 53
4.6.1 Descriptive analysis ..... 53
4.6.2 The Cox regression model and analysis ..... 54
4.6.3 Sensitivity analysis and statistical software ..... 55
4.7 Ethics ..... 57
Chapter 5 ..... 59

5. Results ..... 59

5.1 Article ..... 59

Chapter 6 ..... 83

6. Discussion ..... 83

6.1 Key findings ..... 83

6.2 Strengths and limitations ..... 87

6.3 Clinical and public health implications ..... 89

6.4 Directions for future research ..... 89

Bibliographic References ..... 91

# List of tables

**Table 1. –** Definition of exposure .....47

**Table 2. –** Definition of hospitalization outcomes .....49

**Table 3. –** Definition of neonatal covariates .....51

**Table 4. –** Definition of maternal covariates .....52

**Table 5. –** Incidence of childhood hospitalization according to maternal and infant .....74

**Table 6. –** Intraventricular hemorrhage and incidence of hospitalization for specific childhood disorders .....76

**Table 7. –** Severity of intraventricular hemorrhage and risk of later disorders in childhood .....77

**Table 8. –** Intraventricular hemorrhage and risk of childhood hospitalization in term and preterm infants .....78

**Table 9. –** International Classification of Diseases codes for intraventricular hemorrhage and maternal-infant comorbidity .....79

**Table 10. –** International Classification of Diseases codes for childhood hospitalization outcomes .....80

# List of figures

**Figure 1. –** Cross section of brain and outlying germinal matrix .....28

**Figure 2. –** Conceptual framework for the association of intraventricular hemorrhage and childhood outcomes .....44

**Figure 3. –** Intraventricular hemorrhage and cumulative incidence of childhood hospitalization.....73

# List of abbreviations

| | |
|---|---|
| ART: | Assisted reproductive technology |
| BPD: | Bronchopulmonary dysplasia |
| CIC: | Cumulative incidence curve |
| CIF: | Cumulative incidence function |
| CSF: | Cerebral spinal fluid |
| ELBW: | Extremely low birthweight |
| HR: | Hazard ratio |
| ICD: | The international Classification of Disease |
| ICF: | The International Classification of Functioning Disability and Health |
| IVH: | Intraventricular hemorrhage |
| INSPQ: | Institute National de Santé Publique du Québec |
| Med-Echo: | Maintenance and Use of Data for the Study of Hospital Clientele Registry |
| NEC: | Necrotizing enterocolitis |
| PDA: | Patent ductus arteriosus |
| RAMQ: | Régie d'Assurance Maladie du Québec |
| RDS: | Respiratory distress syndrome |
| ROP: | Retinopathy of prematurity |
| SAS: | Statistical Analysis Software |
| SRY: | Sex determining region Y |
| VLBW: | Very low birthweight |
| WHO: | World Health Organization |
| 95% CI: | 95% confidence interval |

*This thesis is dedicated to the population of infants in the neonatal intensive care unit, their families & the team of healthcare providers that have participated in the clinical management of children with intraventricular hemorrhage.*

# Acknowledgments

Dr. Nathalie Auger I would like to express my sincerest gratitude for your time and contribution towards the progression of my manuscript and thesis. Your medical expertise and clinical insight is invaluable and I have learned a great deal through your exemplary actions. Dr. Auger, you are exceptionally caring and always took the time to support my research interests. Thank you for providing precious coaching and encouragement as it has allowed me to learn and grow. I shall forever remember your words, my mentor.

Aimina Ayoub, I would like to convey my appreciation for your mentorship and time. Thank you for the support dedicated towards teaching me statistical software and honing my epidemiology skills. For continuously being available to review my work & prompt me to become a better learner. I shall cherish your recognition and kindness. My warm wishes to the whole team of the INSPQ for being extremely welcoming and allowing me to have a positive experience.

To my family, thank you for your unconditional support throughout the duration of my studies. Thank you for recognizing my research interests and encouraging me to pursue graduate studies on a topic that I cherish deeply. Your love and support has enabled me to write this thesis. Mandeep, you have been my backbone and my best friend throughout every aspect of my life. You have tremendously supported my career ambitions and allowed me to pursue them. Since the very start I have always felt the encouragement from you and it has kept my motivation strong. Embarking on this graduate journey was not easy and I thank you for all your support. Thank you for serving our country, I salute you.

Lastly, I would like to acknowledge the Jewish General Hospital for having positively changed my life. For providing an environment that shaped my interests, changed my perception on life and enabled me to save lives.

# Chapter 1

## 1. Introduction

Infants with intraventricular hemorrhage (IVH) have an elevated risk of neurodevelopmental disorders, but the association with other childhood morbidities is very poorly understood (1). IVH represents a serious neonatal neurological complication affecting primarily preterm infants (2). This condition is one of the most challenging to clinically manage and frequently implicates end of life decision-making (3). IVH occurs in 20-30% of preterm infants with very low birthweight (1). The pathophysiology is complex and multifactorial (4). The pathogenesis is mainly attributed to hemodynamic instability and vascular weakness of the germinal matrix in the developing brain (2,5). Infants are at increased risk of resuscitation, mechanical ventilation, surgery, and other complications during the neonatal period (6).

Literature on childhood outcomes of IVH focus primarily on neurodevelopmental complications. Affected infants have substantial long-term neurocognitive morbidity (7). These children are at increased risk of cerebral palsy and neurosensory impairments including seizures, language delays, and behavioral disorders (1,8–10). Special educational support may be required at school (11). Almost 85% of infants with severe IVH have major neurocognitive deficiencies with an augmented risk of functional disability and gross motor impairments (8,12). Emerging research is showing that very low birthweight infants with neonatal comorbidities, including IVH, may have higher rates of orthopedic and ophthalmological hospitalizations, but information remains otherwise scarce (13). We sought to capture the extent of the association between IVH and future hospitalization before 12 years of age in a cohort of preterm and term newborns.

# Chapter 2

# 2. Literature review

## 2.1 Definition and descriptive epidemiology

### 2.1.1 Pathophysiology and risk factors of intraventricular hemorrhage

During the neonatal period, infants are susceptible to an array of complications due to their physiological vulnerability. IVH is one such complication affecting upwards of 30% of high risk infants. IVH is described as blood loss from within the ventricular system of the brain. This kind of hemorrhaging is a subtype of intracranial injury (12). In the neonatal intensive care unit, germinal matrix associated IVH is a severe neurological complication. This condition is likely secondary to prematurity and represents the greatest type of central nervous system (CNS) disorder of a preterm birth.

The germinal matrix is a structure that arises during the embryonic period and persists until maturation of cerebral tissue after the infant is born. Significant growth of neuronal and glial precursor cells occurs in this region (5). The germinal matrix represents a site of rapid cellular proliferation with high vascularization and ongoing angiogenesis (14,15). Angiogenesis refers to the sprouting of existing vessels whereas vascularization entails creation of new blood vessels, and both constitute important steps in brain development. Vessels are important channels that supply blood to vital organs throughout the body. There are three types of vessels located in the brain: arteries, veins and capillaries (16). Veins have thinner endothelial walls as compared to arteries and IVH is largely associated to venous-vessel rupturing (5). In the developing and immature cerebrum, vessels can readily rupture due to their anatomical irregularities and large luminal areas (15).

Sophistication in neonatal medical management through use of antenatal steroids, improved ventilator support and postnatal surfactant has positively affected the survival of extremely premature infants (17). Great medical advancements have significantly reduced the age of viability to as low as 22-24 weeks of gestation (18,19). These changes have allowed high risk infants a chance at survival who otherwise would have died. In Canada, between 7-8% of all births are preterm and this number has remained mainly constant over a 10-year span.

High risk deliveries can contribute to an array of factors that may lead to the development of IVH. Low gestational age, birthweight and APGAR scores remain concerning risk factors for the development of IVH. The APGAR score evaluates appearance, pulse, grimace activity and respiration status immediately post birth. It represents an important standardized measure of infant health immediately after birth (15). Sustained low APGAR score at 1 and 5 mins of life is a risk factor for IVH development in the neonate (20).

Prematurity can affect the functioning of various organ systems especially the lungs. Human lung organogenesis starts in the first trimester of pregnancy. Alveolar maturation reaches completion closer to the 35$^{th}$ week of gestation (21,22). Therefore, respiratory insufficiency is predominantly seen in babies born preterm but complications can also arise in term infants (23). Conditions such as respiratory distress syndrome and apnea are exhibited as direct results of prematurity (12). In the case of extremely preterm infants, they may require advance life-sustaining measures such as resuscitation, endotracheal intubation and mechanical ventilation due to reduced lung capacity (14,24). Moreover, these infants often require increased oxygenation in the first 24-hours of life through invasive or non-invasive support to maintain adequate tissue perfusion (12,15). Frequently, endotracheal intubation is maintained through conventional or high-frequency parameters in extremely premature babies (25). In the developing brain, inadequate pulmonary function can result in hypoxia-related tissue injury (16,24). Furthermore, hypoxic injury and fluctuation in systemic blood flow can develop into acid-base imbalances in the body (15,26). Thus, respiratory function plays a dynamic role in the development of IVH. These infants often have substantial physiological instability that require ongoing medical interventions.

Hemodynamic variability and coagulation disorders can contribute to the development of IVH. Hemodynamic variability represents altered perfusion levels in the body related to the cardiopulmonary system. Premature infants frequently exhibit anemia through low red blood cell counts, and thrombocytopenia through low platelet counts related to coagulation irregularities (24,27).When the production of red blood cells is insufficient, it has a direct impact on the tissue oxygenation. Red blood cells carry an important protein called hemoglobin which contains iron and its function is to transport oxygen molecules. It is not uncommon for infants to receive transfusion products to correct their anemic imbalances (28). As a result, hypervolemia (high blood volume) caused by transfusion products can affect systemic blood flow and induce further hemodynamic variability (24,29). Contrarily, hypotension arising from hypovolemia (low blood volume) or cardiac dysfunctions often require use of inotropic medication and volume expanders, which further contribute to systemic blood flow imbalances. Therefore, abrupt

upsurge or drop of systemic blood pressure can affect vessel integrity and cause vessel rupture which contributes to the development of IVH (15,30).

### 2.1.2 Severity of intraventricular hemorrhage

Cerebral ultrasounds and magnetic resonance imaging enables detection and diagnosis of IVH. Testing begins shortly after birth and if IVH is suspected, screening is routinely repeated to monitor progression of disease (31). Head circumference enables a crude measurement of hemorrhagic growth (32). Diagnosis of IVH entails carefully staging the severity of the bleed via the Papile classification which remains the standard medical diagnostic tool (4).

In 1978, Dr. Papile described localized bleeding to the region of the germinal matrix as grade I. The germinal matrix is an area located near the head of the caudate nucleus in the subependymal zone (12). As illustrated in figure 1, the germinal matrix is located centrally in the brain, and in close proximity to the ventricles (33). If hemorrhaging persists, blood can extend into the ventricular system of the brain denoted as grade II. Classification at grade II represents less than 50% of sanguineous ventricular filling. In the context of bleeding progressing beyond the second stage, increased pressure from the excess blood causes ventricular dilation and is classified as grade III. At this point, diagnosis becomes moderate to severe and implies more than 50% of the ventricles are occupied with blood. Hemorrhaging surpassing grade III and extending into the surrounding parenchyma, results in grade IV classification. This last stage is considered the most severe form and results in post-hemorrhagic hydrocephalus or parenchymal infarction (12). Hydrocephalus refers to the accumulation of fluid in the brain due to blockage or obstruction. Parenchymal infarction is caused by severe hypoxic injury and can potentially lead to tissue damage or necrosis (tissue death). The parenchyma is the area outside the ventricles and contains an array of neurons and glial cells. Functional tissue is located in the parenchyma and damage to this area can lead to permanent cognitive impairment (12,15).

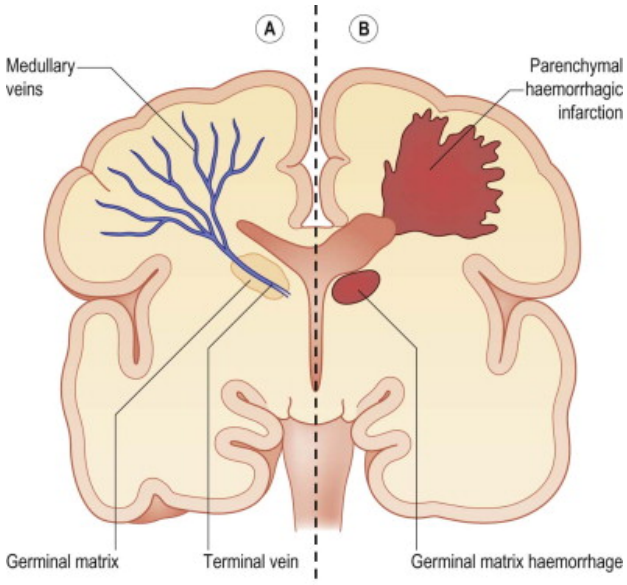



**Figure 1. –** Cross section of brain and outlying germinal matrix (33)

Cerebral spinal fluid (CSF) is important for proper cerebral functioning as it protects the brain, removes waste and provides nutrients. CSF is produced in the ventricles and found within the subarachnoid spaces. The human brain is comprised of four ventricles. Two small lateral ventricles, plus a third and fourth ventricle which allows for the movement and reabsorption of cerebral spinal fluid through channels. In the brain, channels are anatomically known as foramen which are described as "openings" (16). The foramen of Monroe connects the third and fourth ventricle. There exists an anatomical proximity between the germinal matrix and the foramen of Monroe. Closeness of these two structures allows for facilitated introduction of significant blood volume into the ventricular system of the brain. Pathogenesis via this anatomical pathway is viewed in nearly 80% of cases (2,12).

### 2.1.3 Timing of intraventricular hemorrhage

The pathology of IVH can vary as a function of gestational age. Preterm and term infants have distinct risk factors and mechanism of disease. Although, IVH is knowingly more prevalent in preterm infants, cases in term infants do exist. To begin, it is necessary to understand the pathology of IVH in preterm infants. The microvasculature of the subependymal germinal matrix is fragile. During the gestational period, the natural maturation and involution of the germinal matrix starts to occur near the

34-36$^{th}$ week of postconceptional age. This embryonic structure then ceases to appear (24). Angiogenesis and cellular maturation slows down following this vulnerable period of fragility (15). Therefore, preterm infants are more likely to experience germinal matrix associated IVH. Injury to the germinal matrix may impact cellular maturation and migration to cortical regions of the brain (8,12). A subcategory of neuronal cells called pericytes are important players in maintaining the structural integrity of the endothelial tissue surrounding the microvasculature. The presence of intact endothelium helps prevent weakness and bleeding. Without pericytes, there is a reduction in the integrity of cerebral tissue leading to ruptures and breakdowns. It is observed that in preterm infants, there is a reduced density of pericytes in the germinal matrix. A reduction in pericytic action may increase tendency of vessel rupture (5).

In the term infant, IVH is a rare complication, often secondary to traumatic delivery or birth asphyxia (15). Trauma can arise from blunt mechanical force, whereas asphyxia entails severe lack of oxygen to vital parts of the brain. Developmental anomalies or structural faults may also contribute to the risk of IVH in term infants (34). At term, bleeding originates primarily from the choroid plexus as opposed to the subependymal zone. The anatomical location of the choired plexus lies within the ventricles and it also participates in the production of CSF. The germinal matrix does not exist in term infants as it has undergone involution. Vessels tend to have better structural integrity with substantial cellular maturation having already occurred in term infants as compared to preterm (5,12,15).

In 1982, Scher *et al* described an interesting distinction between preterm and term infants with IVH (34). The clinical classification and prognosis of studied cases revealed important structural and anatomical differences. They demonstrated through post-mortem cross-sectional analysis of cerebral tissue that there existed a gestational age induced anatomical difference. Therefore, prediction of clinical outcomes of term infants with the equivalent diagnostic classification as preterm infants should not be alike. In term infants, tissue spasticity in the brain did not vary significantly as the grades of severity increased, unlike preterm infants. Therefore, it was implied that future developmental outcomes of term infants may differ from those of preterm infants. Birth timing is important to understand as etiologic risk factors differ amongst preterm and term infants. At term, hemorrhage inducing elements are related to mechanical and traumatic factors. Contrarily, for preterm it is due to anatomical immaturity and hemodynamic variability (12,34). Term infants may, therefore, have dissimilar developmental outcomes and follow altered pathways compared to preterm (34).

### 2.1.4 Public health implications

Clinical management of infants with IVH can be extensive. Neonatal intensive care and prolonged hospitalizations may be necessary. Depending on the severity of the cases, length of inpatient hospitalization can extend from weeks to months. Conjoined decision-making, in part from the parents and medical staff, is necessary to achieve what is in the best interest for the infant (19). Several interventions and treatments for extremely sick infants aim to maximize future quality of life. Public health wise, healthcare professionals caring for high risk patients can undergo significant emotional and physical repercussions. Emotional and physical taxation on the wellbeing of hospital personnel is common. Ethical and moral distress are two inevitable feelings that develop whilst caring for children with IVH. Viability and futility of care are important topics that arise and can have negative psychosocial effects on everyone involved (19).

Anticipation of high-risk pregnancies and subsequent inpatient hospitalization of sick infants can be better managed through prenatal awareness and teaching. Various determinants of health characterized as maternal risk factors are associated to IVH. Determinants of health are factors that influence the overall health of an individual. Education, lifestyle choices, biology, social factors and income constitute some of the main determinants of health. Variable behaviours, such as smoking, constitute negative lifestyles choices which impose risks to our health and that of others. Each determinant of health can influence each other and affect the overall health of a person and of the people surrounding them.

Universal Medicare is offered to Canadians and it helps subsidize the hefty costs of high risk cases and prolonged hospitalizations. Increased medical management leads to elevation in hospital-related costs, and infrastructure. In Canada, data from the Régie d'Assurance Maladie du Quebec (RAMQ) indicates roughly $123,3 million in hospital associated costs for early preterm, $255,6 million for moderate preterm and $208,2 million for late preterm infants (35). In the United States, lifetime cost of over 4 billion dollars is attributed to the management of infants with IVH (36). High financial needs and psychosocial health of all individuals involved are at stake. Therefore, it is important to get an understanding of immediate and long-term clinical implications of IVH.

## 2.2 Neonatal characteristics

### 2.2.1 Gestational age

The gestational period takes about nine months to complete and is initiated from the moment of conception until the developing fetus achieves full maturation (16). The World Health Organization (WHO) describes term pregnancy as reaching the 37$^{th}$ week of gestation (37). In 2010, 14.1 million babies were born prematurely (38). Globally, 60% of preterm births were found to occur in diverse regions of Africa, India and China. However, this issue is also present in western countries as well. Both low and high-income countries observed substantial rates of preterm births, 9% and 12% respectively. Preterm birth can be sub-classified into three categories: moderate to late preterm (32 to <37 weeks), very preterm (28 to <32 weeks) and extremely preterm (< 28 weeks). In 2016, 7.9% of all Canadian livebirths were considered preterm (39). Nearly 15-20% of infants affected by IVH are born less than 32 weeks of gestation (40). Strikingly, 45% of extremely premature infants (<28 weeks) develop IVH (5,18,40). The prevalence appears to be increasing with the reduction in gestational age. Nonetheless, IVH can also occur in late preterm infants (born 32-36 weeks) but this is uncommon (41). It is evident that prematurity places infants at risk of developing complications in the neonatal period.

### 2.2.2 Birthweight

Birthweight of an infant is a convincing indicator of their health status (42). In the prenatal period, estimated birthweight and growth percentiles classification are routinely measured to assess a developing fetus (15). In the neonatal intensive care unit, medication administration and several hospital protocols are established as a function of birthweight categories. Low birthweight is characterized by less than 2,500 grams (12,15). At times, admission into intensive care can solely be on the basis of low birthweight following delivery. Low birthweight, can be sub-classified into three categories: Very low birthweight or VLBW (<1,500 grams), extremely low birthweight or ELBW (<1,000 grams) (43). In 2012, nearly 22 million babies were born with low birthweight, on a global scale.(44) ELBW infants are at the highest risk for the development of IVH (5,15,45).

### 2.2.3 Infant sex

Sex differentiation is an important checkpoint in development. Sex-specific differences occur at the genetic level and during fetal development. Male fetuses have the sex determining region Y gene (SRY) on their Y chromosome which enables transcription of the male specific sex-genes. By the 5$^{th}$ day of gestation, gonadal tissue starts to form in the fetus (46). Amongst infants born preterm, a sizable portion

are of the male gender (47). In a 2019 study by Batterbe *et al*, findings showed that male infants had higher likelihoods of developing severe morbidity, including IVH (48). In another study by Zhao *et al*, in 2017, conducted within a population of fraternal and identical twins, revealed an increased risk of mortality and negative perinatal outcomes amongst male twins (49). In Canada, there continues to be a higher rate of male preterm birth as compared to females (50).

### 2.2.4 Neonatal comorbidities

Newborn infants diagnosed with IVH are vulnerable to other comorbidities during their hospitalization. Multiple illnesses can affect the pathway to recovery and impact the prognosis of a child (51). Depending on the gestational age, roughly 8% of neonates suffer from major morbidities and nearly half will acquire minor morbidities (52). Six of the most prevalent and serious comorbidities affecting the cardiovascular, respiratory, gastrointestinal and ophthalmologic systems are presented below.

*Patent ductus arteriosus*

From a cardiovascular standpoint, non-closure of patent ductus arteriosus (PDA) remains vastly prevalent in infants born less than 29 weeks of gestation. When the arterial duct (ductus arteriosus) does not close post birth, it causes incorrect shunting of blood between the aorta and the pulmonary artery. The physiological abnormality caused by PDA can lead to systemic hypo-perfusion through mixing of oxygenated and deoxygenated blood (12,15). In 70% of cases, infants are asymptomatic. However, some infants may require surgical ligation to correct this anomaly. Surgical correction can result in mortality and increased susceptibility to infections. Pharmaceutical interventions include administration of indomethacin, a cyclo-oxygenase inhibitor which can lead to heavy kidney and liver side-effects (53).

*Bronchopulmonary dysplasia*

As described previously, premature infants often require fluctuating levels of respiratory support, which lead to respiratory changes in the body. Interventions can be through mechanical ventilation and pharmaceutical means. Common medications include: artificial surfactant, corticosteroids and oxygen. Long-term use these medications and high dependency of external ventilation causes the lung tissue to change overtime. Anatomically, cells begin to exhibit abnormal growth as a function of persistent respiratory failure and increased respiratory effort. Infants begin to develop chronic lung disease known as bronchopulmonary dysplasia (BPD) (12). As the age of viability decreases, surviving preterm infants are at greater risk of developing physiological sequelae of severe BPD long-term. Sequelae can manifest

through form of altered pulmonary function. About 83% may require re-admission in the first two years of life. Additionally, infants with BPD have a higher incidence of developmental delays compared to other children (54).

*Respiratory distress syndrome*

In the neonatal population, inability to achieve adequate respiratory function is common and is a condition known as respiratory distress syndrome (RDS) (12). As affected infants grow, they are frequently screened for pulmonary function abnormalities and obtain neurocognitive evaluations as children (55). Extreme prematurity is a risk factor for respiratory distress syndrome. The preterm infant's lungs are immature, stiff and produce surfactant inefficiently. Specialized type of cells called pneumocytes are found in the lungs and function to produce surfactant. Surfactant is a substance that decreases surface tension in the alveoli which is vital for lung compliance and breathing. Lung immaturity interrelates heavily with cardiopulmonary function which affects cerebral blood flow (26). The cerebral vasoreactivity and autoregulation mechanisms are not completely mature in the developing preterm infant (56).

*Neonatal sepsis*

Infections during the neonatal period can be particularly serious, even resulting in death or severe physiological sequelae. Preterm infants have a further vulnerability to infections due to an immature immune system (12). Immaturity, in part, arises from having a lower production of monocytes and neutrophils. These two cells produce antimicrobial proteins and peptides that help destroy pathogens which is an important step in the initial immune response. Larger quantities of IgG antibodies that help develop immunity are usually transferred to the fetus after the $32^{nd}$ week of gestation (57). Neonatal sepsis can affect quality of life, impair neurodevelopmental progression and trigger clinical stress disorders (58).

*Necrotizing enterocolitis*

Necrotizing enterocolitis (NEC) is a severe gastrointestinal problem seen within the neonatal population. This condition is highly morbid and leads to fatal complications. Nearly 63% of preterm infants can acquire NEC throughout the neonatal period (59). The condition is characterized by ischemic damage to the small intestine which may be irreversible. Injury to the mucosal tissue of the gastrointestinal tract enables bacterial migration and proliferation. An influx of abnormal bacterial outside the natural flora of the intestine can cause pathology and necrosis. Ischemia occurs following periods of hypoxia, which is lack

of oxygen to a given tissue. Impaired gastric acid release, slower intestinal motility and reduced enzyme production can all contribute to gastrointestinal immaturity (12).

*Retinopathy of prematurity*

Retinopathy of prematurity (ROP) is a neonatal comorbidity associated to prolonged oxygenation requirements and other risk factors. The incidence of ROP is about 66% in infants with VLBW. The condition is multifactorial and severe ROP can cause retinal detachment leading to blindness. Other known outcomes of ROP include impaired vision, myopia and strabismus (60,61).

## 2.3 Maternal characteristics

### 2.3.1 Age

Worldwide, women are choosing to have children at older ages (62). On a genetic level, several changes take place, as a function of aging, which affect chromosomal integrity. Telomere shortening, mitochondrial dysfunctions and spindle fiber instability have been shown to occur with increasing age (63). Risk of chromosomal segregation mistakes are higher in women over the age of 35 (64). Advance maternal age has been linked to preterm birth. Increased rates of preterm (<37 weeks) and very preterm births (<32 weeks) have been observed with childbearing ages exceeding 40 years (62,65). Half of preterm births are attributed to advanced maternal age and the use of assisted reproduction technologies (ART) (66).

### 2.3.2 Socioeconomic status

Perinatal health disparities are complex and entail various factors. Deprivation status is affected by the determinants of health. Maternal deprivation can adversely affect perinatal outcomes and pregnancy. Factors associated to maternal deprivation include lifestyle habits, income and education (67). Lifestyle choices such as smoking during pregnancy and reduced education of breastfeeding benefits are seen in women with lower socioeconomic status (68). Women with low income and less education have been associated with increased risk of small-for-gestational-age births (69).

### 2.3.3 Rurality

Geographical location plays a vital role in the provision of health service and resource accessibility. Equitable access to health amenities is critical for the fair access to services (70). Infants born to women living in rural regions have higher risks of birth complications and neonatal mortality rates (71). Rurally located hospitals are often smaller and widely spread apart compared to those in urban regions. Critical

care units are less readily available in the rural sector and have fewer medical subspecialties to treat high risk patients (72).

### 2.3.4 Pregnancy complications

Routine prenatal visits enable women to access the appropriate health resources and receive proper follow-up care throughout their pregnancy. Complications of pregnancy can arise at any point, from conception difficulties to delivery of the baby. Obstetrics and Gynecology is a branch of medicine dedicated to the study and clinical management of maternal-fetal heath (73). Analogous to neonatal morbidities, some well-studied maternal morbidities associated with preterm birth arising during the antenatal period are discussed below. The following pregnancy complications encompass anatomical abnormalities in the placental structures, cardiovascular system, and endocrine changes.

*Placental disorders*

Placental hemorrhage disorders have been associated with early induction of labour (74). The placenta delivers necessary nutrients and allows for oxygen-exchange between the mother and fetus during pregnancy. A tenth of preterm deliveries are related to placenta abruption (75). Placenta abruption is characterized by the detachment of the placenta from the uterine wall, leading to the increased risk of perinatal mortality for the fetus (76). Placenta abruption is a severe complication and is accompanied by bleeding, pain and uterine contractions (75). Premature dissociation of the placenta can cause intra-uterine growth restrictions in the fetus and preterm birth. Placenta previa also arises during pregnancy and contribute to 5% of iatrogenic preterm births. Placenta previa is characterized by the ectopically localized placenta near the lower segment of the uterus, potentially obstructing the cervix resulting in hemorrhaging (73). Furthermore, an abnormal implantation of the placenta creates an unfavorable environment for fetal growth and increases the risk of fetal mal-presentation (76).

*Maternal infection*

Infections during the perinatal period are serious and represent an immense risk factor for the onset of preterm birth. Roughly 30% of preterm births are associated to premature rupture of membranes (76). Chorioamnionitis, an intrauterine infection characterized by inflammation of the chorion and membrane tissue, often results in induction of preterm labour (73). Uterine infections can be caused by cervical incompetence or weakening of the uterine membranes (76). Lack of antenatal steroids, premature

rupture of membrane, intrauterine infection and vaginal delivery are risk factors for the development of IVH (56).

*Gestational diabetes*

To meet the energy demands of the developing fetus the maternal body undergoes significant endocrine changes. Therefore, metabolic fluctuations are expected to occur during pregnancy. The fetal-placental dyad necessitates increased glucose production by the mother due to rapid growth and development. A rise in insulin resistance is natural, in early gestation. However, ongoing elevated levels contribute to the risk of developing diabetes (76). Gestational diabetes mellitus affects almost 5% of all pregnancies. Overall, a tenth of pregnancies are affected by cardiovascular and endocrine conditions (77). Gestational diabetes, hypertension, smoking and the use of ART are maternal risk factors for birth complications (78)

*Hypertensive disorders*

Hypertension disorders can contribute to increased complications during pregnancy, whether they are chronic or induced by gestation itself. Hypertension is characterized by elevated systolic (>120 mmHg) and diastolic (>90 mmHg) pressures. Systolic measures the pressure in the arteries during myocardial contraction and diastolic refers to the pressure during the cardiac relaxation period. Preeclampsia is known as gestational proteinuric hypertension and is a risk factor for preterm birth. Preeclampsia is clinically manifested by elevated blood pressure developing after the $20^{th}$ week of gestation. Eclampsia manifests with the additional onset of seizure activity following the diagnosis of preeclampsia (76).

## 2.4 Current knowledge of intraventricular hemorrhage outcomes

### 2.4.1 Long-term neurodevelopmental outcomes

Infants affected by IVH are at high risk for adverse neurodevelopmental outcomes later in life (7–9,40). To further understand this pathophysiology, it is imperative to comprehend the design of the brain. The central nervous system is comprised of the brain and the spinal cord. In the brain, the cerebral cortex consists of four lobes; frontal, parietal, occipital and temporal. They contain intricate neuronal networks that are associated with higher cerebral functioning and complex neurosensory pathways. Each area of the brain constitutes distinct functions and is associated to unique motor, behaviour and sensory

responses (16). Consequences of brain injury depend heavily on the affected area. The prognosis and spectrum of future outcomes varies according to the extent of the hemorrhage and localization (unilateral or bilateral). Lower impact bleeding in preterm infants has been associated with a 16% reduction in the volume of cortical grey matter as compared to infants born at term (79).

*Learning and cognition*

Cognition refers to the ability to comprehend, manipulate and process information into thoughts, otherwise known as neurocomputation (80). The Bayley Scale of Infant Development is a standardized tool used to assess neurodevelopment. The Cognition Bayley Scale 3$^{rd}$ edition provides a functional scoring test for children between the ages of 1-42 months. The cognitive score assesses 5 main categories: cognition, language, motor, social-emotional and adaptive skills (81). The Bayley Scale 2$^{nd}$ edition is a standardized framework for the mental development index score. Similarly, the mental development index also assesses 5 main categories: memory, knowledge, problem solving, language and sensory-perception (82).

Learning aptitude is intricately linked with cognition. The frontal lobe and other subcortical areas of the cerebral cortex are associated to learning and memory functions. Injury to vital regions of the brain can negatively affect knowledge processing, learning and retention (83). Upwards of 75% of infants with severe hemorrhage experience prominent learning disabilities and often require special needs at school (5). Mental retardation is commonly observed in children with severe IVH. Evidence of reduced mental capacity usually becomes more prominent as children reach the ages between 2-9 years (79).

In a study by Payne *et al*, an increased risk of adverse outcomes was seen with severe IVH. However, infants with mild IVH were not associated to have adverse neurodevelopment impairments between the ages of 18-22 months. Infants with severe hemorrhage have been associated to lower Bayley language and cognitive scores as compared to mild hemorrhage (9). On a positive note, about 15% of infants diagnosed with severe grades of IVH can later have normal neurodevelopment during childhood (84). However, infants with ventriculoperitoneal shunts had lower gross-motor function and cognitive scores during childhood (79).

*Neurosensory and motor impairments*

Sensation is classified into multiple sensory groups; visual, auditory, olfactory, tactile and pain stimuli. In the context of long-term outcomes, infants with IVH have been linked to having primarily visual impairments and hearing deficiencies. Visual dysfunctionality is defined by low visual acuity scores of less

than 6/60 using the metric scale and bilateral blindness. The Snellen chart allows for standardised diagnosis of visual acuity by measuring the sharpness of image resolution (16). Partial or complete visual loss can be linked to morbidities such as ROP (84). Hearing abnormality were mainly associated to cochlear impairments and the need of hearing implants at 7-8 months of age (1,8). Hearing deficiencies mainly pertained to middle ear or cochlear disorders (85).

Neurosensory assessment is routinely evaluated in children. In a study by Reubsaet *et al*, in 2017, infants with severe IVH living with sensory impairments had normal MRI results. Their MRI results showed almost no abnormality in cerebral lesions or very subtle white matter irregularities (85). Bolisetty *et al*, in 2014, showed that the incidence of neurosensory impairment augments as the severity of IVH increases; 17.6% (grade I) versus 40% (grade IV) (8). In this same study, neurosensory impairment was defined as blindness, hearing loss, cerebral palsy and a low mental development index (8).

Cerebral palsy and mental retardation have been profoundly linked to IVH. Cerebral palsy is chronic neurological disability which is characterized by atypical motor movements. This condition can lead to a lifelong handicap whilst severely impairing daily functioning and heavily affecting quality of life (86). Severe grades III and IV are associated to a 5.9 increased odds of cerebral palsy (8). In 2006, Futagi *et al* observed a cohort of preterm infants with severe hemorrhage born less than 31 weeks in which 71% developed cerebral palsy. Epilepsy and hydrocephalus are adverse complications of IVH. Grades I and II exhibit a significantly lower risk of epilepsy (5%), whereas the risk was 40% in infants with grade IV (84). The period between the initial onset of hemorrhaging to its full clinical manifestation can leave infants susceptible to other neonatal complications. Overall, some infants with minor bleeds can survive without substantial disability while others may endure sensory impairments, and mental retardation later in childhood (12,20).

### 2.4.2 Long-term morbidity

Research encompassing IVH pertains mainly to neurodevelopmental disorders in childhood. The understanding of how IVH poses a risk to other morbidities later in life is largely unknown. A large void of knowledge around mechanism of action and impact on various physiological systems of the body are under researched. Ventricular hemorrhage of this nature is multifactorial and may implicate diverse parts of the brain. There is a need to explore this hemorrhagic brain injury and its association to other childhood outcomes. Much of the literature investigates morbidity in preterm cohorts affected by multiple neonatal complications without a sole focus on IVH. There are very little studies conducted on such associations.

### 2.4.3 Mortality

Infant mortality rates have dropped in developed countries due to the sophistication of perinatal medicine. Obstetrical and gynecological practices can better manage high risk pregnancies and monitor maternal-fetal health (76). Despite this positive change, preterm infants are still susceptible to early mortality. Roughly 10% of all neonatal deaths are attributed to IVH. Furthermore, almost half of all infants below the gestational age of 25 weeks, with severe IVH, usually die. Similarly, 61% of infants weighing <750 grams will most likely pass away following a diagnosis of IVH. Risk of mortality appears to increase with the severity of the bleed. A 4:1 incidence of mortality is seen in infants with severe grades of hemorrhaging versus those with mild grades (75). This further highlights a need for proper critical care management and better clinical practices surrounding IVH cases.

## 2.5 Summary of literature review

IVH is one of the most severe complications arising during the neonatal period. Preterm and term infants are both susceptible to the development of IVH through different pathological pathways. Differences are associated to physiological immaturity and structural anomalies. Future prognosis of an infants is a function of hemorrhagic severity. These infants are susceptible to early neonatal death and adverse short and long-term outcomes. Infants often experience prolonged hospitalization, resulting in difficult clinical management. At times, ethical considerations regarding futility of care and questions surrounding end-of-life decisions are warranted. Moreover, the full extent of physiological or neurodevelopment damage cannot be predicted which leads to uncertainty and worry for the healthcare providers and families as they face difficult choices ahead.

Infants with IVH can exhibit a wide range of neurodevelopmental impairments later in life. Impairments range from neurosensory losses to severe motor function diseases like cerebral palsy. Infants often require special educational needs throughout early childhood and experience cognitive delays. A life with physical and mental handicap can result in a lower quality of life and affect activities of daily living. However, the association between IVH and other childhood outcomes is poorly understood. This project will help determine how IVH is associated with non-neurodevelopmental outcomes in childhood. Better comprehension of future needs can enable improved clinical management, offer appropriate support to promote family resilience and improve decision-making.

## 2.6 Research objectives

*To determine the associational between neonatal IVH and future hospitalization in childhood.*

The aim of this study is to determine if IVH is associated with a higher risk of adverse childhood morbidity before 12 years of age. The proposed research will investigate the hypothesis that children born with IVH will have a higher risk of hospitalization-related morbidity later in childhood compared with infants who do not have IVH.

The specific question is:

1) What is the association between IVH and future causes of child hospitalization?

# Chapter 3

## 3. Conceptual framework

A conceptual framework allows to understand and illustrate known factors in given relationship using standardized language and concepts. It allows for comprehensive synergy of data. The International Classification of Functioning Disability and Health (ICF) is a known bio-psychosocial framework that enables understanding of health and disability (87). The ICF is a standardized framework and regroups multiple concepts that contribute to the measurement of disability and functioning. Body structure, activities, participation and environmental factors are major concepts that aggregate to provide a holistic picture of one's health (87,88). The ICF framework was a good fit for my project as it helps guide better decision-making for families of children affected by neurological disorders. We can explore concepts such quality of life and functional capacities as a function of personal and environmental risk factors that affect the future of children.

The conceptual framework created for this study (Figure 2) for the association of IVH and later childhood outcomes, is adapted from the ICF model. This framework corresponded to a good fit because IVH represents a serious neurological condition causing both physical and mental impediments. It has a grave effect on future disability, functioning and health. In my framework, neonatal and maternal characteristics corresponded to environmental and personal factors that can affect the association. These two set of characteristics are drawn from known biological risk factors and determinants of health. Although, the outcomes in my study focus on physiological systems, they indirectly affect health practices and psychosocial well-being of families and healthcare providers.

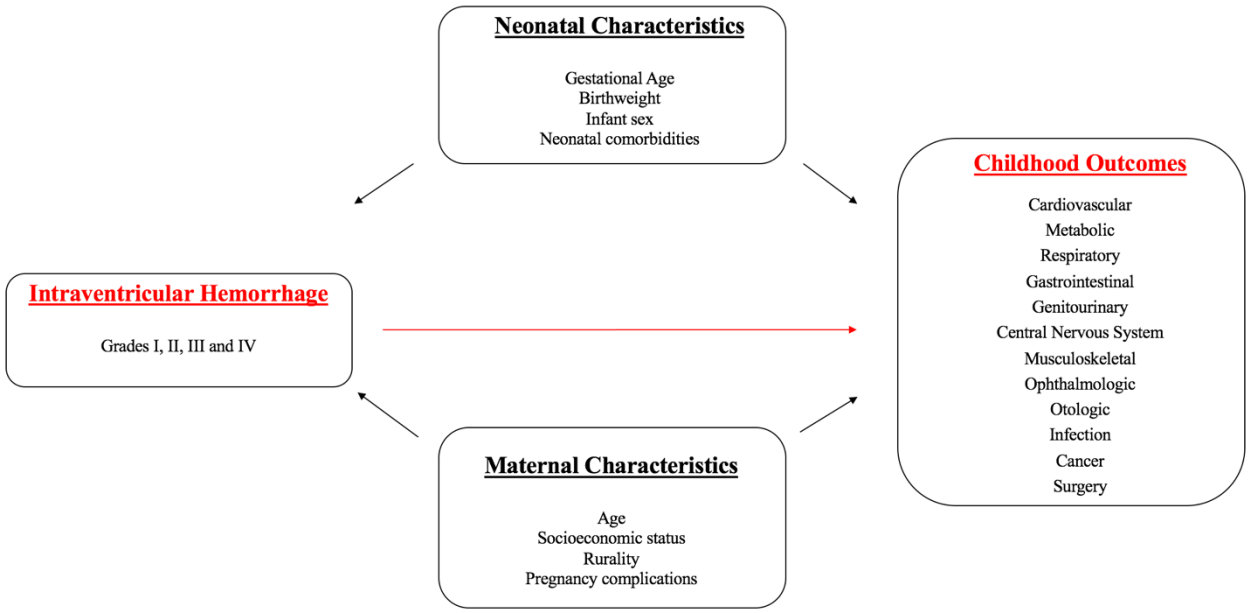





**Figure 2. –** Conceptual framework for the association of intraventricular hemorrhage and childhood outcomes

# Chapter 4

# 4. Methods

## 4.1 Context and study design: Analysis of secondary data

A retrospective cohort was chosen to be the ideal study design for this research project. IVH is a rare condition only seen in a small fraction of neonates, therefore, obtaining data retrospectively enabled us to maximise the number of cases. The data was drawn from Québec's Maintenance and Use of Data for the Study of Hospital Clientele registry (Med-Echo), a dataset covering hospitalizations for the entire province. Med-Echo has been used in past research projects to study the outcomes of newborns with morbidity (6). Furthermore, 99% of all births in the province of Quebec occur in hospital settings (89). Demographic and diagnostic medical reports of each patient are kept archived and public medical data is readily used for perinatal research (90).

Discharge summaries for all infants born in hospitals between April 2006 and March 2016 in the province of Québec were utilized. Discharge summaries in Med-Echo are validated through rigorous algorithms and contain up to 41 clinical diagnostic and 35 procedural codes (90). Scrambled medical health insurance numbers were used to track infants through time, for a total follow-time of 12 years. Subsequent re-hospitalizations were identified for specific outcomes pertinent to the objective of this study.

## 4.2 Population and exclusion criteria

The total population consisted of all infants born, in hospitals, in the province of Quebec, Canada (n= 846,267) and non-hospital births were excluded. The population consisted of the total number of infants with IVH (n=1,322). Population data was derived from Med-Echo and was therefore representative of the population of newborns in the province. Newborns infants of all gestational ages were included. Gestational age and birthweight correlations were verified for fetal-growth discrepancies using Alexander's method; infants abnormally too small or large for their gestational age were excluded (n= 2140) (91). Infants who died before discharge were also excluded (n=2997). Lastly, infants with invalid or missing medical health insurance numbers were excluded due to inability to follow them through-time (n=56603). The final retrospective cohort study population consisted of 794,384 newborns in Québec, Canada.

**Summary of exclusion criteria:**

1. Non-hospital births
2. Infants born with an invalid or missing medical health insurance number
3. Implausible gestational age and birthweight
4. Infants who died before discharge

## 4.3 Definition of exposure

The main exposure measure was IVH during the neonatal period (Table 1). Cases of IVH were captured from either the birth hospitalization or occurring after transfer to a tertiary hospital. The 10$^{th}$ revision of the International Classification of Diseases (ICD) was used to identify exposed infants. Diagnostic codes ranging from P52.0 to P52.3 were selected from the perinatal section of the ICD (92). Grades III and IV represent physiologically distinct stages of the disease but are coupled in the ICD coding (n=194). Milder forms of IVH, grade I (n= 811) and grade II (n=185) were available separately. IVH is routinely detected using cerebral ultrasound or magnetic resonance imaging in Quebec hospitals (4,31). The information on the type of modality used for detection was not available in our database. Once exposed cases were identified via the diagnostic codes, they were regrouped as a binary variable (yes, no). IVH associated to trauma or accidents were separately available in the ICD but were not included. Coding of the IVH variable has not been validated but it has been demonstrated for other diagnostic codes from the ICD such as BPD (93).

To capture the severity of disease, the exposure was stratified into different grades (I, II, III/IV, and unspecified) using the Papile classification system (Table 1). The Papile system remains the standard of practice for the clinical diagnosis of IVH in infants (4). The worsening spectrum of neurodevelopmental disorders has shown to have a proportional association with higher grades of IVH (2,8,9,12). Therefore, it was important to create a stratification to understand the differences in outcomes as they relate to severity.

Preterm (n=51,324) and term (n=743,060) infants can both be affected by IVH through distinct pathological pathways. In preterm infants, the disease arises from the subependymal germinal matrix of the brain, due to immaturity of the CNS and hemodynamic instability (2,4,12). For infants born at term, hemorrhaging originates primarily from the choroid plexus and is likely unrelated to immaturity. Due to dissimilar pathologies, our study assessed a four-level composite variable capturing the association for

outcomes of interest as they relate to gestational age. Stratification was defined as: preterm IVH (n=1,139), term IVH (n=183), preterm with no IVH (n=50,185) and term with no IVH (n=742,877).

**Table 1. –** Definition of exposure

| | International Classification of Diseases 10th Revision |
|---|---|
| Intraventricular hemorrhage | |
| **Grade I**<br>*Localized to germinal matrix* | P52.0 |
| **Grade II**<br>*Extension to ventricles (<50%)* | P52.1 |
| **Grade III/IV**<br>*Ventricular dilation (≥50%) and parenchymal infarction* | P52.2 |
| **Grade unspecified**<br>*Undetermined classification* | P52.3 |

## 4.4 Definition of outcomes

To define the outcomes, physiological systems of the body were selected on the basis of routinely managed clinical disorders in children. A total of 12 categories were created (Table 2). The 10$^{th}$ revision of the International Classification of Diseases (ICD) was used to identify 10 categories of outcomes (92). For the category of cancer, a vast selection of topography and morphology codes were selected from the International Classification of Diseases for Oncology-3 (94). Surgical outcomes were selected on the basis of re-admission requiring use of general anesthesia from the Canadian Classification of Health Interventions (CCI) codes (95). Procedures from outpatient ambulatory clinics and those requiring local anesthesia were not included. Each category was defined as a binary variable (yes/no). A final variable was created to designate *any* outcome if the infant exhibited at least 1 future hospitalization. The focus of this study was to examine outcomes in later childhood that were beyond the scope of neurodevelopmental disorders.

Given the heavy association of IVH to negative neurocognitive sequelae, I chose to sub-classify the CNS category based on known complications of IVH. Neurological conditions in the CNS category included meningitis, hydrocephalus, cerebral palsy and other CNS disorders mainly related to connective tissues impairments.

For the remainders of the categories, a range of physiological outcomes were chosen. Respiratory disorders and infections such as asthma, pneumonia and influenza are routinely managed conditions in pediatric hospitals. The respiratory syncytial virus is a serious pathogen that affects children in early infancy (96–101). Worldwide, obesity, diabetes and malnutrition are important conditions that affect millions of children (102–104). Genitourinary conditions such as nephritis and renal failure are kidney diseases are managed in the pediatric population (105,106). Juvenile arthritis is a serious impairment and represents the most common autoimmune disorder negatively affecting the quality of life in children (107). Moving on to visual impairments, strabismus often affects children (60). Retinal detachment and breaks can lead to visual impairment including blindness, although these are less common, they nonetheless have an impact on activities of daily living. Auditory disorders such as otitis media, ear effusion and otalgia are commonly seen childhood disorders (108–110). According to the Canadian health agency, childhood infections are common, thus vaccine preventable diseases were included (111). Arrhythmias, cardiac infections and other cardiovascular disorders can occur in children (12,15,16). Functional gastrointestinal disorders are serious and heavily affect the pediatric population (112).

**Table 2. –** Definition of hospitalization outcomes

| | International Classification of Diseases 10th Revision |
|---|---|
| Cardiovascular | |
| Acute rheumatic fever | I00-I01 |
| Primary pulmonary hypertension | I27.0 |
| Pericarditis, endocarditis, myocarditis | I30, I32, I33, I39, I40, I41 |
| Cardiomyopathy | I42, I43 |
| Other cardiovascular and conduction disorders | I44-I49 |
| Supraventricular/ventricular tachycardia | I47.1, I47.2 |
| Atrial fibrillation | I48.0 |
| Heart failure | I50 |
| Atherosclerosis | I70 |
| Hypotension | I95 |
| Cardiac murmurs | R01 |
| Respiratory | |
| Acute upper respiratory infections | J0 |
| Influenza and pneumonia | J1 |
| Respiratory syncytial virus | B97.4, J12.1, J20.5, J21.0 |
| Other acute lower respiratory infections | J2 |
| Asthma | J45 |
| Pneumonitis due to solids and liquids | J69.0 |
| Metabolic | |
| Diabetes mellitus | E10-E14 |
| Malnutrition | E40-E46 |
| Obesity | E65, E66 |
| Gastrointestinal | |
| Esophagus, stomach, duodenal disorders | K20-K31 |
| Non-infective enteritis and colitis | K50-K52 |
| Acute appendicitis | K35 |
| Umbilical hernia | K42 |
| Hepatic failure and liver disease | K71-K72 |
| Acute pancreatitis | K85 |
| Abdominal and pelvic pain | R10 |
| Genitourinary | |
| Nephritis | N10-N12 |
| Renal failure | N17-N19 |
| Central nervous system | |
| Cerebral palsy | G80 |
| Meningitis | G00-G03 |
| Hydrocephalus | G91 |
| Other disorders | G12, G40, G41, G47.30 |
| Musculoskeletal | |
| Arthritis | M05-M09 |
| Scoliosis | M41 |

| | |
|---|---|
| Systemic connective tissue disorders | M30-M36 |
| Ophthalmologic | |
| Strabismus | H49-H50 |
| Ptosis of eyelid | H02.4 |
| Lacrimal stenosis | H04.5 |
| Retinal detachments and breaks | H33 |
| Disorders of optic nerve and visual pathways | H46-H48 |
| Visual impairment including blindness | H54 |
| Otologic | |
| Otitis media | H65, H66, H67 |
| Otalgia and effusion | H92 |
| Infection | |
| Vaccine-preventable infections | B01, A36, A37, A33, B06, A08, B26, B05, A80 |
| Cellulitis | L03 |
| Erythema infectiosum | B08.3 |
| Scarlet fever | A38 |

| | **International Classification of Childhood Cancer 3rd Edition** |
|---|---|
| Cancer | Topographic and morphology codes |

| | **Canadian Classification of health interventions Volume III** |
|---|---|
| Surgery | General Anesthesia codes |

## 4.5 Definition of covariates

*Neonatal characteristics*

Environmental and physical factors can affect an association for a particular exposure measure and outcome. The neonatal characteristics chosen in this study were used as covariates to control for the association of IVH and later childhood hospitalization. Infant gestational age and birthweight were both stratified into four categories, as per the WHO guidelines (Table 3). Gender was coded as a binary variable: female (n=386,738) or male (n=407,601). Neonatal comorbidities, as described in the literature review, were extracted using codes from the ICD. The final variable for neonatal comorbidity was a binary exposure (yes/no) if the infant exhibited at least 1 comorbidity (yes, n=17,485).

**Table 3. –** Definition of neonatal covariates

| | International Classification of Diseases 10th Revision |
|---|---|
| Neonatal comorbidity | |
| Bronchopulmonary dysplasia | P27.1 |
| Respiratory distress syndrome | P22.0 |
| Necrotizing enterocolitis | P77 |
| Patent ductus arteriosus | Q25.0, P29.3 |
| Sepsis | J95.88, P35, P36, P52.1 |
| Retinopathy of prematurity | H35.1 |

| | Stratification |
|---|---|
| Gestational age | <28, 28- 31, 32-36, ≥37 weeks |
| Birthweight | <1000, 1000-1499, 1500-2499, ≥2500 g |
| Infant sex | Male, female |

*Maternal characteristics*

The maternal characteristics chosen in this study were used as covariates to control for the association of IVH and later childhood hospitalization (Table 4). Maternal age and socioeconomic deprivation were stratified into three categories. Rurality was classified as a binary variable (rural or urban). Time period was stratified into three categories and based on the financial period. Pregnancy complications as described in the literature review, were extracted using codes from the ICD. The final variable for maternal comorbidity was a binary exposure (yes/no) if the mother exhibited at least 1 pregnancy complication (yes, n=138,139).

**Table 4. –** Definition of maternal covariates

| | International Classification of Diseases 10th Revision |
|---|---|
| Pregnancy complications | |
| Gestational diabetes | O24.8 |
| Preeclampsia | O11, O13, O14, O15 |
| Placental abruption | O45 |
| Placenta previa | O44 |
| Sepsis | O41.12, O41.13, O75.3 |

| | Stratification |
|---|---|
| Maternal age | <25, 25-34, ≥35 years |
| Socioeconomic deprivation | Upper, lower quintile* |
| Rurality | Urban, rural |
| Time period | 2006-2009, 2010-2012, 2013-2015 |

*Lower quintile represents the most materially deprived fifth of the population. Socioeconomic deprivation was determined according to neighborhood income, employment, and education (113).

## 4.6 Data analysis

### 4.6.1 Descriptive analysis

The epidemiological approach begins with descriptive data. To obtain frequencies, the initial number of infants with IVH and those later hospitalized was determined for each outcome and covariate. A total of 245,065 infants were re-hospitalized for *any* outcome, of which 886 corresponded to infants with IVH. The incidence rates for all new cases of IVH for *any outcome* was calculated using the two formulae described below for the exposed and unexposed populations.

**Incidence rate in exposed population:**

$$\text{Incidence Rate}_{\text{per 1,000}} = \frac{\text{Total number of new hospitalized cases in the exposed population}}{\text{Total person-years in the exposed population}} \times 1000$$

**Incidence rate in unexposed population:**

$$\text{Incidence Rate}_{\text{per 1,000}} = \frac{\text{Total number of new hospitalized cases in the unexposed population}}{\text{Total person-years in the unexposed population}} \times 1000$$

The formula utilizes a time-dependent denominator that accounts for the contribution of time from each infant due to individual length variations. A person-year denomination was used because of a lengthy follow-up time extended up to 12 years. The contributed time from each infant was included up until they acquired the event, died or the study ended. The incidence rates for *any* hospitalization was computed per 1,000 person-years with a 95% confidence interval (CI) (Table 5).

The cumulative incidence was calculated for the exposed and unexposed populations as described in the two formulae below. Cumulative incidence curve (CIC) was then plotted, by outcome category, to illustrate the difference of re-hospitalization amongst infants with IVH and no IVH, for a total of 12 years of follow-up (Figure 3).

**Cumulative incidence in exposed population:**

$$\text{Cumulative Incidence}_{\text{per 1,000}} = \frac{\text{Total number of cases in the exposed population}}{\text{No. of people at risk at the start of the observation period}} \times 1000$$

**Cumulative incidence in unexposed population:**

$$\text{Cumulative Incidence}_{\text{per 1,000}} = \frac{\text{Total number of cases in the unexposed population}}{\text{No. of people at risk at the start of the observation period}} \times 1000$$

The cumulative incidence for *any* hospitalization was computed per 1,000 person-years with a 95% CI for all covariates (Table 5). The cumulative incidence function aims to depicts the incidence of an event occurring given the presence of competing risks (114). Cumulative incidence function curves are alternatives to Kaplan Meier plots in determining marginal probability when competing risks are present (115).

### 4.6.2 The Cox regression model and analysis

The Cox proportional hazards regression is a mathematical model used for the analysis of survival data. The Cox regression model is robust and can approximate the parametric model well. In theory, the cox model is defined as a hazard function, which aims to describe the hazard for an individual at time ($t$) based on a set of predictor time-independent variables. The formula presented below consists of $h_0$ depicting the baseline hazard function and the exponentiation of the linear sum of $B_1X_i$ (115).

$$h(t, \mathbf{X}) = h_0(t)e^{\sum_{i=1}^{p} \beta_i X_i}$$

In our study, we obtained the risk values using **the measure of effect** which is otherwise known as the hazard ratio (HR). This measure of effect, described below, can be obtained without knowing the baseline hazard function $h_0(t)$. HR can be obtained by the exponentiation of the regression coefficient ($B_1$).

$$\widehat{HR} = e^{\hat{\beta}_1}$$

To obtain a 95% CI for the association of IVH with later childhood hospitalizations, we used the formula below. The level of significance was kept at 0.05 and the CI was calculated around each regression coefficient.

$$\exp\left[\hat{\beta}_1 \pm 1.96\sqrt{\hat{Var}\hat{\beta}_1}\right]$$

The first admission for each outcome was used and the number of days since birth as the time-scale. Infants who were never hospitalized for the outcomes of interest were censored. Death was accounted for as a competing event using the Fine and Gray method. The Fine and Gray method is a sub-distribution function of the cox proportional hazard regression model. The extended model accounts for the use of time-dependent variables and is used for the analysis of time-to-event outcomes (114,115).

The proportional hazard (PH) assumption for the Cox regression is important in order to validate the model. The assumption is met if the hazard remains constant over time, implying the use of time-independent predictor variables. Fine and Gray exploits the CIC that enable the PH assumption to be satisfied through time-dependent variables, as seen in our study (115).

The HR was calculated for the association of IVH and later hospitalization outcomes. The model was adjusted for maternal age, pregnancy complications, infant sex, neonatal comorbidities, birthweight, socioeconomic deprivation, and year of birth (Table 6). The unadjusted model was computed using only the binary IVH exposure for all outcomes. In secondary analyses, we assessed the relationship between the different grades of IVH and hospitalization outcomes in adjusted Cox models (Table 7). We verified whether the associations differed between term and preterm infants (Table 8). We accounted for infants with the same mother using the robust sandwich estimator. The variance-covariance sandwich estimator is well known for parametric cox models (115,116).

### 4.6.3 Sensitivity analysis and statistical software

Sensitivity analysis enables evaluation of robustness of a model through alterations in study design (117). To evaluate the validity of our findings, different covariates were chosen to test our model. Since

birthweight and gestational age are two strong indicators of infant health, we conducted several models with variations of this coupling: only gestational age, both gestational age and birthweight, excluding both and only birthweight. The interaction of these two variables can share a conjoined effect that impacts the statistical relationship. We also conducted the sensitivity analyses by time period, ranging from 2006 to 2015.

Data was analyzed in statistical analysis software (SAS) v9.4 (SAS Institute Inc., Cary, NC). The high computational power of SAS allows the software to analyze and handle large quantities of data (118).

## 4.7 Ethics

This study did not require the direct participation of research subjects. The criteria for this study fell under an exception from the Tri-council Policy Statement:

Article 2.2 of chapter 2; criteria (a)

"*The information is legally accessible to the public and appropriately protected by law*"

We received an ethics waiver from the University of Montreal Hospital Centre's institutional review board which deemed ethics review was not needed due to use of a de-identified administrative dataset.

# Chapter 5

# 5. Results

## 5.1 Article

Kaur, A. Luu, TM., Shah, PS., Ayoub, A., Auger, N. Neonatal intraventricular hemorrhage and hospitalization in childhood. Pediatric Neurology. In press. 2019

### Manuscript Details

| | |
|---|---|
| **Manuscript number** | PNU_2019_452 |
| **Title** | Neonatal intraventricular hemorrhage and hospitalization in childhood |
| **Article type** | Research Paper |


**Abstract**

Background: Intraventricular hemorrhage is a serious neonatal complication associated with neurodevelopmental disorders, but the relationship with other childhood morbidities is unclear. Objective: We sought to assess the association of neonatal intraventricular hemorrhage with the risk of childhood morbidity up to 12 years of age. Methods: We analyzed a longitudinal cohort of 794,384 infants born between 2006 and 2016 in Quebec, Canada, with 4,269,579 person-years of follow-up over 12 years. The exposure was grade I to IV intraventricular hemorrhage in the neonatal period. The main outcome measure was childhood hospitalization by cause of admission. In adjusted Cox regression models, we estimated hazard ratios and 95% confidence intervals (CI) for the association of intraventricular hemorrhage with future hospitalization in childhood. Results: The incidence of childhood hospitalization was higher in infants with intraventricular hemorrhage than in infants without hemorrhage (23.8 vs. 5.7 per 100 person-years). Compared with no hemorrhage, infants with intraventricular hemorrhage had 1.56 times the risk of hospitalization (95% CI 1.43-1.70). The risk was 2.81 times higher for grade III/IV hemorrhage (95% CI 2.23-3.53). Intraventricular hemorrhage at term was associated with 3.19 times the risk of hospitalization (95% CI 2.55-4.00), whereas preterm intraventricular hemorrhage was associated with 1.82 times the risk (95% CI 1.66-2.00), compared with no hemorrhage at term. Primary reasons for hospitalizations included central nervous system, ophthalmologic, musculoskeletal, and cardiovascular disorders. Conclusions: Intraventricular hemorrhage, especially of higher grades and in term neonates, is an important determinant of the future risk of child hospitalization.



| | |
|---|---|
| **Keywords** | Cerebral hemorrhage; Hospitalization; Infants, premature; Longitudinal studies Morbidity; Term birth |
| **Manuscript region of origin** | North America |



| | |
|---|---|
| **Corresponding Author** | Nathalie Auger |
| **Corresponding Author's Institution** | National Public Health Institute of Quebec, University of Montreal |
| **Order of Authors** | Amarpreet Kaur, Thuy Mai Luu, Prakesh Shah, Aimina Ayoub, Nathalie Auger |


### Submission Files Included in this PDF

**File Name [File Type]**

PEDN_Kaur_Cover letter.docx [Cover Letter]

PEDN_Kaur_Manuscript.docx [Manuscript File]

PEDN_Kaur_Figure 1.tif [Figure]

To view all the submission files, including those not included in the PDF, click on the manuscript title on your EVISE Homepage, then click 'Download zip file'.

### Research Data Related to this Submission

There are no linked research data sets for this submission. The following reason is given:
The authors do not have permission to share data

**Neonatal intraventricular hemorrhage and hospitalization in childhood**

Amarpreet Kaur RN MSc,[1,2] Thuy Mai Luu MD MSc FRCPC,[3] Prakesh S. Shah MD,[4,5] Aimina Ayoub MSc,[2,6] Nathalie Auger MD MSc FRCPC[1,2,6]

[1]Department of Social and Preventive Medicine, University of Montreal, Montreal, Quebec, Canada

[2]Institut national de santé publique du Québec, Montreal, Quebec, Canada

[3]Department of Pediatrics, Sainte-Justine University Hospital Research Centre, University of Montreal, Montreal, Quebec, Canada

[4]Department of Pediatrics, University of Toronto, Mount Sinai Hospital, Toronto, Canada

[5]Institute of Health Policy, Management and Evaluation, University of Toronto, Toronto, Canada

[6]University of Montreal Hospital Research Centre, Montreal, Quebec, Canada

Running title: Intraventricular hemorrhage and childhood outcomes

Correspondence to: Dr Nathalie Auger, 190 Cremazie Blvd E., Montreal, Quebec H2P 1E2, Canada, Tel: 514-864-1600 ext. 3717, Fax: +1.514.864.1616, Email: nathalie.auger@inspq.qc.ca

Counts: Abstract 244, Manuscript 2497, References 27, Figures 1, Tables 4, Supplemental Tables 2

**ABSTRACT**

**Background**: Intraventricular hemorrhage is a serious neonatal complication associated with neurodevelopmental disorders, but the relationship with other childhood morbidities is unclear.

**Objective**: We sought to assess the association of neonatal intraventricular hemorrhage with the risk of childhood morbidity up to 12 years of age.

**Methods**: We analyzed a longitudinal cohort of 794,384 infants born between 2006 and 2016 in Quebec, Canada, with 4,269,579 person-years of follow-up over 12 years. The exposure was grade I to IV intraventricular hemorrhage in the neonatal period. The main outcome measure was childhood hospitalization by cause of admission. In adjusted Cox regression models, we estimated hazard ratios and 95% confidence intervals (CI) for the association of intraventricular hemorrhage with future hospitalization in childhood.

**Results**: The incidence of childhood hospitalization was higher in infants with intraventricular hemorrhage than in infants without hemorrhage (23.8 vs. 5.7 per 100 person-years). Compared with no hemorrhage, infants with intraventricular hemorrhage had 1.56 times the risk of hospitalization (95% CI 1.43-1.70). The risk was 2.81 times higher for grade III/IV hemorrhage (95% CI 2.23-3.53). Intraventricular hemorrhage at term was associated with 3.19 times the risk of hospitalization (95% CI 2.55-4.00), whereas preterm intraventricular hemorrhage was associated with 1.82 times the risk (95% CI 1.66-2.00), compared with no hemorrhage at term. Primary reasons for hospitalizations included central nervous system, ophthalmologic, musculoskeletal, and cardiovascular disorders.

**Conclusions**: Intraventricular hemorrhage, especially of higher grades and in term neonates, is an important determinant of the future risk of child hospitalization.

**Keywords**: Cerebral hemorrhage; Hospitalization; Infants, premature; Longitudinal studies Morbidity; Term birth

## INTRODUCTION

Infants with intraventricular hemorrhage have an elevated risk of neurodevelopmental disorders,[1] but the association with other childhood morbidities is very poorly understood. Intraventricular hemorrhage is a serious neonatal neurological complication affecting primarily preterm infants.[2] Intraventricular hemorrhage occurs in 20-30% of preterm infants with very low birth weight.[1] Although complex and multifactorial, the pathogenesis of intraventricular hemorrhage is mainly attributed to hemodynamic instability and vascular weakness of the germinal matrix in the developing fetal brain.[2,3]

Literature on childhood outcomes of intraventricular hemorrhage focuses primarily on neurodevelopmental complications.[1,4–6] These children are at increased risk of cerebral palsy and neurosensory impairment, including seizures, language delay, and behavioral disorders.[1,4–6] Special educational support may be required at school.[7] Emerging research is showing that very low birth weight infants with neonatal comorbidities, including intraventricular hemorrhage, may have higher rates of orthopedic and ophthalmological hospitalizations,[8] but data remain otherwise scarce. We sought to capture the extent of association between intraventricular hemorrhage and future hospitalization up to 12 years of age in a cohort of preterm and term newborns.

## METHODS

### Study design and population

We conducted a retrospective cohort study of 794,384 neonates born in hospitals of Quebec, Canada, between 2006 and 2016. Using scrambled health insurance numbers, we followed the infants over time for up to 12 years after birth to identify future hospitalizations. Follow-up began at birth and ended on March 31, 2018. We acquired data on the infants from hospital discharge abstracts in the Maintenance and Use of Data for the Study of Hospital Clientele registry, a dataset encompassing all hospitalizations in Quebec.[9] Each discharge summary is coded and validated by trained personnel and contains up to 41 clinical diagnostic and 35 procedural codes.[9]

The cohort was restricted to infants born at term or preterm who survived to neonatal discharge. We excluded infants with intraventricular hemorrhage who were withdrawn from life support and newborns with implausible gestational age.[10] We also excluded infants with invalid health insurance numbers, as we could not obtain follow-up data. We had no information on births at home or in birthing centers, but 99% of deliveries in Quebec occur in hospital. The cohort was therefore representative of the population of

newborns in the province.

**Intraventricular hemorrhage**

The main exposure measure was intraventricular hemorrhage in the neonatal period, whether at birth or after transfer to a tertiary hospital. We used the diagnostic codes P52.0 to P52.3 from the 10th revision of the International Classification of Diseases (ICD) to identify infants with intraventricular hemorrhage. We analyzed intraventricular hemorrhage as a binary exposure (yes, no). In Quebec, intraventricular hemorrhage is detected using cerebral ultrasound or magnetic resonance imaging.[11] Information on the modality used for detection was not available in our database. We did not include intraventricular hemorrhage due to trauma or accidents.

We further categorized intraventricular hemorrhage by grade (I, II, III/IV, unspecified), following the Papile classification system.[12] Grade I encompasses mild bleeding confined to the germinal matrix, a vascularized area of the brain close to the ventricles.[12] Grade II includes hemorrhage in the ventricles without dilation of the ventricular system.[12] Grade III is hemorrhage that results in ventricular dilation, and Grade IV refers to parenchymal hemorrhagic infarction.[12] In our data, grades III and IV hemorrhage, the most severe forms, were only available as a combined code in the ICD (Table 9). The ICD follows the Papile classification system but does not distinguish grades III and IV.

We considered the possibility that the impact of intraventricular hemorrhage in infants born at term differs from preterm. In preterm infants, intraventricular hemorrhage arises in the subependymal germinal matrix due to immaturity of the central nervous system and hemodynamic instability.[2,3] Intraventricular hemorrhage in infants born at 37 weeks or more, in contrast, originates primarily from the choroid plexus and is likely unrelated to immaturity.[13] Owing to the distinct pathophysiology of intraventricular hemorrhage in preterm and term infants, we assessed a 4-level variable capturing preterm hemorrhage (<37 weeks), term hemorrhage (≥37 weeks), preterm without hemorrhage, and term without hemorrhage.

**Outcomes**

The main outcome measure was childhood hospitalization by type of admission. We selected conditions generally managed in a clinical context, which we grouped by system: cardiovascular, respiratory, metabolic, gastrointestinal, genitourinary, central nervous system, musculoskeletal, ophthalmologic, otologic, infection, and cancer. We used ICD codes to identify admissions for these disorders (Table 10).

For cancer, we used morphology and topography codes from the International Classification of Diseases for Oncology-3.[14] Moreover, we identified infants who underwent surgical procedures under general anesthesia. We could not identify mild disorders treated in ambulatory clinics.

**Covariates**

We accounted for several covariates, including maternal age at birth (<25, 25-34, ≥35 years), pregnancy complications (gestational diabetes, preeclampsia, placental abruption, placenta previa, sepsis; Table 9), infant sex (male, female), neonatal comorbidity (bronchopulmonary dysplasia, respiratory distress syndrome, necrotizing enterocolitis, patent ductus arteriosus, sepsis, retinopathy of prematurity; Table 9), birth weight (<1000, 1000-1499, 1500-2499, ≥2500 grams), preterm birth (<28, 28-31, 32-36, ≥37 weeks of gestation), socioeconomic deprivation (most disadvantaged fifth of the population, not disadvantaged, unspecified), and year of birth (2006-2009, 2010-2012, 2013-2016).[15] Socioeconomic deprivation was determined using census data on neighborhood income, employment, and education.[16]

**Data Analysis**

We computed the incidence rate of hospitalization, as well as the cumulative incidence after 12 years of follow-up, accounting for death as a competing event. We used Cox proportional hazards regression models to calculate hazard ratios (HR) and 95% confidence intervals (CI) for the association of intraventricular hemorrhage with later childhood hospitalizations. We assessed the first admission for each outcome and used the number of days since birth as the time scale. We censored infants who were never hospitalized for the outcomes of interest and accounted for death as a competing event using the Fine and Gray method.[17] We verified the proportional hazards assumption in log (-log survival) plots. We accounted for infants with the same mother using the robust sandwich estimator,[18] and adjusted the associations for maternal age, pregnancy complications, infant sex, neonatal comorbidity, birth weight, socioeconomic deprivation, and year of birth.

In secondary analyses, we assessed the relationship between the different grades of intraventricular hemorrhage and hospitalization outcomes in adjusted Cox models. We verified whether the associations varied between term and preterm infants. We carried out sensitivity analyses for the relationship between intraventricular hemorrhage and later childhood outcomes by time period. We also examined Cox models that were additionally adjusted for preterm birth, and not adjusted for either preterm birth or birth weight.

Data were analyzed in SAS v9.4 (SAS Institute Inc., Cary, NC). We received an ethics waiver from the University of Montreal Hospital Centre's institutional review board which deemed ethics review was not needed due to use of a de-identified administrative dataset.

**RESULTS**

In this cohort of 794,384 infants with 4,269,579 person-years of follow-up, 1,322 infants (0.2%) were diagnosed with intraventricular hemorrhage (Table 5). A total of 245,065 infants were later hospitalized during childhood, for an incidence of 23.8 hospitalizations per 100 person-years in infants with intraventricular hemorrhage (95% CI 22.3-25.4) and 5.7 in infants without hemorrhage (95% CI 5.7-5.8). Infants with grade III/IV intraventricular hemorrhage had an even higher incidence of hospitalization (49.5 per 100 person-years, 95% CI 42.4-57.8). Preterm and term infants with intraventricular hemorrhage both had elevated hospitalization rates.

Infants with intraventricular hemorrhage had a high cumulative incidence of all outcomes (Figure 3). There was a rapid increase in incidence of most hospitalization outcomes in the first 4 years of life, followed by a steady but slower progression until 6 years of age onwards. Infants with intraventricular hemorrhage had an early divergence of incidence for nearly all outcomes, compared with no hemorrhage. Differences in hospitalization for musculoskeletal disorders, however, only began to appear towards 8 years of age.

In adjusted Cox models, intraventricular hemorrhage was associated with 1.56 times the risk of hospitalization overall (95% CI 1.43-1.70), compared with no hemorrhage (Table 6). Infants with intraventricular hemorrhage had 4.20 times the risk of central nervous system (95% CI 3.43-5.13), 3.01 times the risk of ophthalmologic (95% CI 2.32-3.89), and 2.43 times the risk of cardiovascular disorders (95% CI 1.93-3.05). Weaker but statistically significant associations were also present for respiratory, gastrointestinal, genitourinary, otologic, and infectious diseases, as well as surgery.

Infants with severe intraventricular hemorrhage had the greatest risk of hospitalization (Table 7). Compared with no hemorrhage, grade III/IV intraventricular hemorrhage was associated with 2.81 times the risk of hospitalization for any outcome (95% CI 2.23-3.53), whereas grade I and II were associated with 1.34 (95% CI 1.21-1.49) and 1.51 (95% CI 1.22-1.87) times the risk, respectively. A similar trend was apparent for most specific outcomes. Infants with grade III/IV hemorrhage had a particularly elevated risk of central nervous system (HR 14.36, 95% CI 10.62-19.42), musculoskeletal (HR 13.22, 95% CI 5.34-32.73),

ophthalmologic (HR 7.87, 95% CI 5.31-11.67), cardiovascular (HR 5.19, 95% CI 3.53-7.64), and genitourinary hospitalization (HR 4.22, 95% CI 2.43-7.32). Intraventricular hemorrhage was also associated with the risk of cancer, although the number of events was low.

Associations between intraventricular hemorrhage and later childhood outcomes were somewhat stronger for infants born at term than preterm (Table 8). Intraventricular hemorrhage at term was associated with 3.19 times the risk of hospitalization for any outcome (95% CI 2.55-4.00), whereas preterm intraventricular hemorrhage was associated with 1.82 times the risk (95% CI 1.66-2.00), compared with no hemorrhage at term. Term infants with intraventricular hemorrhage were especially more likely than preterm infants, with or without hemorrhage, to be hospitalized for central nervous system, cardiovascular, ophthalmologic, and musculoskeletal disorders. Stratifying the analyses by time period did not affect the associations, nor did adding preterm birth or removing preterm birth and birth weight from the adjusted regression models.

**DISCUSSION**

In this longitudinal cohort study with 4.3 million person-years of follow-up, children with neonatal intraventricular hemorrhage had an elevated risk of hospitalization for a range of disorders up to 12 years of age. Associations were particularly prominent for central nervous system, ophthalmologic, cardiovascular, and musculoskeletal disorders. The associations were stronger for grade III/IV hemorrhage and term hemorrhage. This study provides novel evidence that children with intraventricular hemorrhage are at risk of morbidity beyond neurodevelopmental outcomes, including hospitalization for a wide range of disorders that may significantly impact family dynamics and quality of life.

Intraventricular hemorrhage is one of the most challenging neonatal morbidities to manage and frequently implicates ethically difficult end-of-life decisions that are influenced by long-term prognosis and predicted quality of life.[19] However, future outcomes of infants with intraventricular hemorrhage are rather poorly understood, as previous literature has mainly focused on developmental and cognitive sequelae.[1,4–6] In a cohort of 1,472 infants born before 27 weeks of gestation in the United States, severe intraventricular hemorrhage was associated with 3.43 times the odds of cerebral palsy, 1.68 times the odds of neurodevelopmental impairment, and 2.51 times the odds of motor delay at 18-22 months of age, compared with no hemorrhage.[5] Associations appear to be weaker or absent for low grade intraventricular hemorrhage.[4–6]

In our study, intraventricular hemorrhage was associated with hospitalization for a range of childhood disorders, including central nervous system, ophthalmologic, musculoskeletal, and cardiovascular outcomes. Associations were present regardless of severity but were stronger for grade III/IV hemorrhage. To our knowledge, comparable data from other studies do not exist, thus it is difficult to determine whether similar effects would be present in other study populations. The closest studies examined the association of severe intraventricular hemorrhage with the risk of rehospitalization before 18 years of age in a cohort of 6,385 infants with very low birth weight.[8,20] The investigators found that infants with intraventricular hemorrhage had a 2-fold greater risk of future hospitalization compared with no hemorrhage.[20] A separate analysis of the same cohort reported that intraventricular hemorrhage was associated with 14 times the risk of neurosurgical hospitalization, and an increased risk of orthopedic and ophthalmologic hospitalization.[8] However, the results may not generalize to all infants with intraventricular hemorrhage as the cohort was restricted to neonates weighing 1500 grams at birth and only assessed grade III/IV hemorrhage.

In our study, intraventricular hemorrhage was associated with childhood hospitalization in both preterm and term infants. In preterm infants, the pathophysiology of intraventricular hemorrhage relates to vascular immaturity in the subependymal germinal matrix where neuronal and glial precursor cells are found.[2,3] At low gestational ages, injury to this region may impact neuronal cell maturation and migration to cortical brain regions where higher level neuronal functioning occurs.[2–4] At term, however, intraventricular hemorrhage is primarily due to bleeding from the choroid plexus. Intraventricular hemorrhage at term is rare and often secondary to traumatic delivery or birth asphyxia, although a small fraction is due to developmental and anatomical anomalies or severe stress.[13] In our data, hemorrhage was more strongly associated with childhood hospitalization in term than preterm infants, but unmeasured confounders may have inadvertently attenuated the associations for preterm neonates.[21]

The association of intraventricular hemorrhage with such a wide range of childhood disorders may relate to the clinical course of these infants. Preterm neonates with intraventricular hemorrhage may have other neonatal complications, including bronchopulmonary dysplasia, retinopathy of prematurity, or severe necrotizing enterocolitis, which can increase medical vulnerability.[15] Children with bronchopulmonary dysplasia are at risk of respiratory infections or impaired pulmonary function.[22] Retinopathy of prematurity is associated with complications such as strabismus,[23] and necrotizing enterocolitis with feeding problems or short bowel syndrome that may require surgical interventions.[24] Although we adjusted for these

neonatal comorbidities, we cannot eliminate the possibility that they influence the risk of future disorders. Intraventricular hemorrhage may itself lead to morbidity through various mechanisms depending on hemorrhage location and possible immune system involvement.[25,26] Furthermore, infants with intraventricular hemorrhage are at risk of neurological disorders such as cerebral palsy.[1,4–6] Overall, these children are medically complex and difficult to manage.[27] Anticipating the future health needs of infants with intraventricular hemorrhage, including those with medical complexity, can help improve care coordination and provide families with adequate support.

This study has several limitations. As we used hospital discharge abstracts, we had limited data on maternal smoking and other potential confounders, and therefore cannot rule out residual confounding. The severity of intraventricular hemorrhage can change throughout the course of an infant's hospitalization, which may lead to exposure misclassification. Although rigorous algorithms are used to validate Quebec hospital data, non-differential misclassification due to coding errors may have occurred and attenuated associations.[9] Cancer, musculoskeletal, and metabolic disorders were rare, and associations with these outcomes should be interpreted with caution. We had no information on neurodevelopmental outcomes. This study only accounted for childhood disorders that required hospitalization, and generalizability to other aspects of childhood morbidity that do not necessitate admission remains unclear.

**CONCLUSION**

The findings of this study suggest that neonatal intraventricular hemorrhage, especially severe hemorrhage and hemorrhage at term, is associated with an increased risk of hospitalization for a range of disorders in childhood. Affected infants have a greater risk of central nervous system, ophthalmologic, musculoskeletal, and cardiovascular hospitalization. The findings may help healthcare providers counsel parents and provide opportunities to anticipate future care needs, as well as support care coordination and family resilience.

**Acknowledgments**: The authors thank Sophie Grand'Maison MD at the University of Montreal Hospital Research Centre, Montreal, Canada for helpful comments on the manuscript.

**Funding**: This work was supported by the Canadian Institutes of Health Research [grant number PJT-162300]; and the Fonds de recherche du Québec-Santé [grant number 34695]. The study sponsors were not involved in study design; in the collection, analysis and interpretation of the data; in the writing of the report; and in the decision to submit the article for publication.

**Declarations of interest**: None.

**REFERENCES**

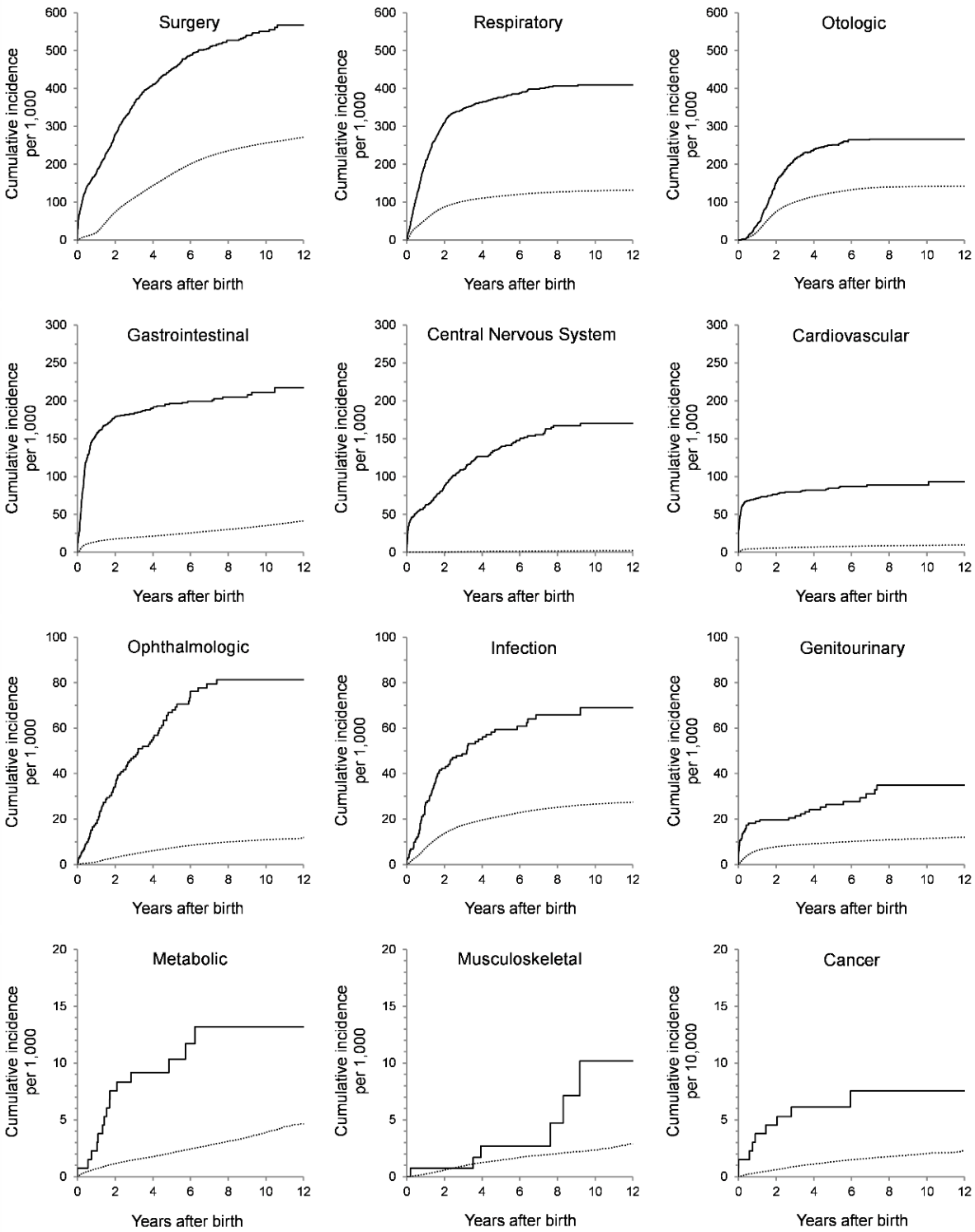

1. Mukerji A, Shah V, Shah PS. Periventricular/intraventricular hemorrhage and neurodevelopmental outcomes: a meta-analysis. Pediatrics 2015;136:1132–43.
2. Volpe JJ. Intraventricular hemorrhage in the premature infant—current concepts. Part I. Ann Neurol 1989;25:3–11.
3. Ballabh P. Intraventricular hemorrhage in premature infants: mechanism of disease. Pediatr Res 2010;67:1–8.
4. Bolisetty S, Dhawan A, Abdel-Latif M, Bajuk B, Stack J, Lui K. Intraventricular hemorrhage and neurodevelopmental outcomes in extreme preterm infants. Pediatrics 2014;133:55–62.
5. Payne AH, Hintz SR, Hibbs AM, Walsh MC, Vohr BR, Bann CM, et al. Neurodevelopmental outcomes of extremely low-gestational-age neonates with low-grade periventricular-intraventricular hemorrhage. JAMA Pediatr 2013;167:451–9.
6. Patra K, Wilson-Costello D, Taylor HG, Mercuri-Minich N, Hack M. Grades I-II intraventricular hemorrhage in extremely low birth weight infants: effects on neurodevelopment. J Pediatr 2006;149:169–73.
7. van de Bor M, den Ouden L. School performance in adolescents with and without periventricular-intraventricular hemorrhage in the neonatal period. Semin Perinatol 2004;28:295–303.
8. Kuint J, Lerner-Geva L, Chodick G, Boyko V, Shalev V, Reichman B. Type of re-hospitalization and association with neonatal morbidities in infants of very low birth weight. Neonatology 2019;115:292–300.
9. Ministry of Health and Social Services. Med-Echo System Normative Framework - Maintenance and use of data for the study of hospital clientele. Quebec: Government of Quebec; 2017.
10. Alexander GR, Himes JH, Kaufman RB, Mor J, Kogan M. A United States national reference for fetal growth. Obstet Gynecol 1996;87:163–8.

11. Brouwer AJ, Groenendaal F, Benders MJ, de Vries LS. Early and late complications of germinal matrix-intraventricular haemorrhage in the preterm infant: what is new? Neonatology 2014;106:296–303.
12. Papile LA, Burstein J, Burstein R, Koffler H. Incidence and evolution of subependymal and intraventricular hemorrhage: a study of infants with birth weights less than 1,500 gm. J Pediatr 1978;92:529–34.
13. Scher MS, Wright FS, Lockman LA, Thompson TR. Intraventricular hemorrhage in the full-term neonate. Arch Neurol 1982;39:769–72.
14. Steliarova-Foucher E, Stiller C, Lacour B, Kaatsch P. International Classification of Childhood Cancer, third edition. Cancer 2005;103:1457–67.
15. Linder N, Haskin O, Levit O, Klinger G, Prince T, Naor N, et al. Risk factors for intraventricular hemorrhage in very low birth weight premature infants: a retrospective case-control study. Pediatrics 2003;111:e590–5.
16. Pampalon R, Hamel D, Gamache P, Simpson A, Philibert MD. Validation of a deprivation index for public health: a complex exercise illustrated by the Quebec index. Chronic Dis Inj Can 2014;34:12–22.
17. So Y, Lin G, Johnston G. Using the PHREG procedure to analyze competing-risks data [Internet]. Cary, NC: SAS Institute Inc.; 2014.
18. Lin DY, Wei LJ. The robust inference for the Cox proportional hazards model. J Am Stat Assoc 1989;84:1074–8.
19. Brecht M, Wilkinson DJ. The outcome of treatment limitation discussions in newborns with brain injury. Arch Dis Child Fetal Neonatal Ed 2015;100:F155–60.
20. Kuint J, Lerner-Geva L, Chodick G, Boyko V, Shalev V, Reichman B. Rehospitalization through childhood and adolescence: association with neonatal morbidities in infants of very low birth

weight. J Pediatr 2017;188:135–141.e2.

21. Whitcomb BW, Schisterman EF, Perkins NJ, Platt RW. Quantification of collider-stratification bias and the birthweight paradox. Paediatr Perinat Epidemiol 2009;23:394–402.
22. Baraldi E, Filippone M. Chronic lung disease after premature birth. N Engl J Med 2007;357:1946–55.
23. Page JM, Schneeweiss S, Whyte HE, Harvey P. Ocular sequelae in premature infants. Pediatrics 1993;92:787–90.
24. Frost BL, Modi BP, Jaksic T, Caplan MS. New medical and surgical insights into neonatal necrotizing enterocolitis: a review. JAMA Pediatr 2017;171:83–8.
25. Kamel H, Iadecola C. Brain-immune interactions and ischemic stroke: clinical implications. Arch Neurol 2012;69:576–81.
26. Zhang J, Shi K, Li Z, Li M, Han Y, Wang L, et al. Organ- and cell-specific immune responses are associated with the outcomes of intracerebral hemorrhage. FASEB J 2018;32:220–9.
27. Cohen E, Kuo DZ, Agrawal R, Berry JG, Bhagat SK, Simon TD, et al. Children with medical complexity: an emerging population for clinical and research initiatives. Pediatrics 2011;127:529–38.

**Figure 3. –** Intraventricular hemorrhage and cumulative incidence of childhood hospitalization




*Solid line, intraventricular hemorrhage; Dotted line, no hemorrhage

**Table 5. –** Incidence of childhood hospitalization according to maternal and infant characteristics

| | No. infants | No. hospitalized | Incidence rate per 100 person-years (95% CI) | Cumulative incidence per 100 at 12 years (95% CI) |
|---|---|---|---|---|
| Intraventricular hemorrhage | | | | |
| All grades | 1,322 | 886 | 23.8 (22.3-25.4) | 74.7 (71.1-77.9) |
| Grade I | 811 | 507 | 19.7 (18.1-21.5) | 69.8 (65.2-73.9) |
| Grade II | 186 | 128 | 27.8 (23.4-33.1) | 78.4 (65.8-86.8) |
| Grade III/IV | 194 | 159 | 49.5 (42.4-57.8) | 89.6 (75.6-95.8) |
| Grade unspecified | 131 | 92 | 25.1 (20.4-30.7) | 78.6 (65.8-87.0) |
| No | 793,062 | 244,179 | 5.7 (5.7-5.8) | 37.5 (37.4-37.7) |
| Intraventricular hemorrhage and preterm birth | | | | |
| Hemorrhage/preterm | 1,139 | 768 | 24.0 (22.4-25.8) | 75.0 (71.2-78.4) |
| Hemorrhage/term | 183 | 118 | 22.5 (18.8-26.9) | 72.3 (61.4-80.6) |
| No hemorrhage/preterm | 50,185 | 21,172 | 9.0 (8.9-9.1) | 48.7 (48.1-49.3) |
| No hemorrhage/term | 742,877 | 223,007 | 5.5 (5.5-5.6) | 36.8 (36.6-36.9) |
| Maternal age, years | | | | |
| <25 | 127,201 | 44,889 | 6.7 (6.6-6.7) | 42.6 (42.2-43.0) |
| 25-34 | 531,485 | 164,891 | 5.8 (5.7-5.8) | 37.6 (37.4-37.8) |
| ≥35 | 135,698 | 35,285 | 4.8 (4.8-4.9) | 32.5 (32.1-32.9) |
| Pregnancy complications* | | | | |
| Yes | 138,139 | 43,679 | 6.3 (6.3-6.4) | 39.3 (38.8-39.7) |
| No | 656,245 | 201,386 | 5.6 (5.6-5.7) | 37.2 (37.1-37.4) |
| Infant sex | | | | |
| Male | 407,601 | 141,957 | 6.7 (6.7-6.8) | 42.1 (41.8-42.3) |
| Female | 386,783 | 103,108 | 4.8 (4.7-4.8) | 32.9 (32.6-33.1) |
| Neonatal comorbidity† | | | | |
| Yes | 17,485 | 8,318 | 11.1 (10.9-11.4) | 53.5 (52.4-54.4) |
| No | 776,899 | 236,747 | 5.6 (5.6-5.7) | 37.2 (37.1-37.4) |
| Birth weight, grams | | | | |
| <1000 | 1,693 | 1,185 | 24.3 (23.0-25.7) | 74.3 (71.6-76.7) |
| 1000-1499 | 3,292 | 1,890 | 15.9 (15.2-16.7) | 63.2 (61.0-65.3) |
| 1500-2499 | 34,255 | 13,820 | 8.6 (8.5-8.8) | 47.8 (47.0-48.7) |
| ≥2500 | 755,144 | 228,170 | 5.6 (5.6-5.6) | 36.9 (36.8-37.1) |
| Preterm birth, weeks | | | | |
| <28 | 1,624 | 1,160 | 26.3 (24.8-27.8) | 75.8 (73.0-78.3) |
| 28-31 | 4,012 | 2,297 | 15.7 (15.1-16.4) | 63.1 (61.2-64.9) |
| 32-36 | 45,688 | 18,483 | 8.4 (8.3-8.6) | 47.1 (46.4-47.7.) |
| ≥37 | 743,060 | 223,125 | 5.5 (5.5-5.6) | 36.8 (36.6-37.0) |
| Socioeconomic deprivation | | | | |
| Yes | 157,152 | 50,700 | 6.1 (6.1-6.2) | 39.6 (39.2-40.0) |
| No | 606,565 | 185,402 | 5.6 (5.6-5.7) | 37.1 (36.9-37.3) |
| Year of birth†† | | | | |
| 2006-2009 | 306,967 | 112,465 | 5.0 (4.9-5.0) | 38.2 (38.0-38.4) |
| 2010-2012 | 245,459 | 75,650 | 5.9 (5.9-5.9) | 33.3 (33.0-33.5) |
| 2013-2015 | 241,958 | 56,950 | 7.9 (7.8-7.9) | 27.9 (27.7-28.2) |

| | | | | |
|---|---|---|---|---|
| Total | 794,384 | 245,065 | 4.5 (4.4-4.5) | 37.6 (37.4-37.8) |

[*]Gestational diabetes, preeclampsia, placental abruption, placenta previa, and sepsis

[†]Bronchopulmonary dysplasia, respiratory distress syndrome, necrotizing enterocolitis, patent ductus arteriosus, sepsis, and retinopathy of prematurity

[††] Infants born towards the end of study exhibited a shorter follow-up time

**Table 6. –** Intraventricular hemorrhage and incidence of hospitalization for specific childhood disorders

| | Intraventricular hemorrhage | | No hemorrhage | | Hazard ratio (95% CI)* | |
|---|---|---|---|---|---|---|
| | No. infants | Incidence rate per 1,000 person-years (95% CI) | No. infants | Incidence rate per 1,000 person-years (95% CI) | Unadjusted | Adjusted† |
| Cardiovascular | 114 | 14.2 (11.9-17.1) | 6,452 | 1.2 (1.2-1.2) | 11.45 (9.48-13.82) | 2.43 (1.93-3.05) |
| Respiratory | 508 | 86.4 (79.2-94.2) | 95,379 | 19.2 (19.1-19.3) | 3.85 (3.53-4.20) | 1.43 (1.30-1.58) |
| Metabolic | 15 | 1.8 (1.1-2.9) | 2,227 | 0.4 (0.4-0.4) | 4.25 (2.56-7.07) | 1.30 (0.74-2.29) |
| Gastrointestinal | 263 | 37.4 (33.1-42.2) | 22,371 | 4.2 (4.1-4.2) | 8.25 (7.27-9.37) | 1.56 (1.35-1.81) |
| Genitourinary | 38 | 4.5 (3.3-6.2) | 8,179 | 1.5 (1.5-1.5) | 2.87 (2.08-3.95) | 1.65 (1.15-2.36) |
| Central nervous system | 192 | 24.9 (21.6-28.7) | 8,583 | 1.6 (1.5-1.6) | 15.24 (13.16-17.65) | 4.20 (3.43-5.15) |
| Cerebral palsy | 57 | 6.8 (5.3-8.8) | 432 | 0.1 (0.1-0.1) | 84.82 (64.31-111.9) | 4.78 (3.21-7.13) |
| Meningitis | 27 | 3.2 (2.2-4.6) | 1,091 | 0.2 (0.2-0.2) | 15.25 (10.39-22.38) | 6.12 (3.38-11.08) |
| Hydrocephalus | 61 | 7.3 (5.7-9.4) | 238 | 0.04 (0.04-0.05) | 160.8 (121.3-213.2) | 43.03 (20.64-89.72) |
| Other | 94 | 11.5 (9.4 -14.0) | 7,145 | 1.3 (1.3-1.3) | 8.54 (6.97-10.47) | 2.71 (2.08-3.53) |
| Musculoskeletal | 6 | 0.7 (0.3-1.6) | 1,433 | 0.3 (0.2-0.3) | 2.62 (1.18-5.83) | 2.01 (0.90-4.50) |
| Ophthalmologic | 91 | 11.1 (9.0-13.6) | 6,773 | 1.2 (1.2-1.3) | 8.72 (7.08-10.73) | 3.01 (2.32-3.89) |
| Otologic | 328 | 46.7 (41.9-52.0) | 102,153 | 22.1 (22.0-22.2) | 2.11 (1.90-2.36) | 1.19 (1.06-1.34) |
| Infection | 80 | 9.9 (7.9-12.3) | 18,259 | 3.4 (3.3-3.4) | 2.76 (2.21-3.45) | 1.53 (1.20-1.96) |
| Cancer | 9 | 1.1 (0.5-2.0) | 1,240 | 0.2 (0.2-0.2) | 4.55 (2.36-8.76) | 5.03 (2.18-11.61) |
| Surgery | 623 | 113.0 (104.5-122.3) | 160,603 | 33.5 (33.3-33.7) | 3.27 (3.00-3.56) | 1.59 (1.44-1.75) |
| Any | 886 | 238.1 (222.9-254.3) | 244,179 | 57.2 (57.0-57.5) | 3.65 (3.38-3.94) | 1.56 (1.43-1.70) |

*Hazard ratios are for intraventricular hemorrhage relative to no hemorrhage

†Adjusted for maternal age, pregnancy complications, infant sex, neonatal comorbidity, birth weight, socioeconomic deprivation, and year of birth

**Table 7. –** Severity of intraventricular hemorrhage and risk of later disorders in childhood

| | Grade I hemorrhage | | Grade II hemorrhage | | Grade III/IV hemorrhage | |
|---|---|---|---|---|---|---|
| | No. of infants | Hazard ratio (95% CI)* | No. of infants | Hazard ratio (95% CI)* | No. of infants | Hazard ratio (95% CI)* |
| Cardiovascular | 56 | 1.98 (1.48-2.67) | 15 | 1.77 (1.03-3.05) | 34 | 5.19 (3.53-7.64) |
| Respiratory | 285 | 1.29 (1.14-1.46) | 84 | 1.56 (1.25-1.95) | 88 | 1.75 (1.40-2.19) |
| Metabolic | 7 | 1.01 (0.46-2.21) | 5 | 2.60 (1.01-6.68) | <5 | 1.84 (0.58-5.84) |
| Gastrointestinal | 140 | 1.38 (1.15-1.67) | 49 | 1.74 (1.29-2.34) | 56 | 2.31 (1.71-3.12) |
| Genitourinary | 15 | 1.07 (0.63-1.83) | 7 | 1.88 (0.86-4.11) | 14 | 4.22 (2.43-7.32) |
| Central nervous system | 65 | 2.31 (1.75-3.05) | 22 | 2.81 (1.78-4.43) | 77 | 14.36 (10.62-19.42) |
| Cerebral palsy | 22 | 3.07 (1.86-5.09) | 5 | 2.39 (0.94-6.05) | 24 | 14.78 (8.72-25.06) |
| Meningitis | 6 | 2.25 (0.88-5.75) | <5 | 5.61 (1.83-17.22) | 12 | 19.61 (9.35-41.14) |
| Hydrocephalus | 7 | 8.00 (2.86-22.37) | <5 | 13.83 (3.50-54.55) | 46 | 259.0 (123.2-544.3) |
| Other | 37 | 1.79 (1.26-2.56) | 15 | 2.49 (1.45-4.28) | 25 | 4.89 (3.14-7.64) |
| Musculoskeletal | <5 | 0.55 (0.08-3.76) | - | - | 5 | 13.22 (5.34-32.73) |
| Ophthalmologic | 32 | 1.76 (1.20-2.57) | 15 | 3.00 (1.78-5.07) | 33 | 7.87 (5.31-11.67) |
| Otologic | 202 | 1.21 (1.05-1.40) | 54 | 1.28 (0.98-1.69) | 44 | 1.07 (0.79-1.46) |
| Infection | 47 | 1.49 (1.10-2.01) | 13 | 1.60 (0.89-2.88) | 13 | 1.75 (1.00-3.03) |
| Cancer | 6 | 5.41 (2.14-13.68) | <5 | 8.34 (1.68-41.33) | <5 | 4.34 (0.53-35.46) |
| Surgery | 342 | 1.35 (1.20-1.52) | 90 | 1.45 (1.15 (1.84) | 129 | 3.18 (2.50-4.05) |
| Any | 507 | 1.34 (1.21-1.49) | 128 | 1.51 (1.22-1.87) | 159 | 2.81 (2.23-3.53) |

*Hazard ratios are for intraventricular hemorrhage relative to no hemorrhage, adjusted for maternal age, pregnancy complications, infant sex, neonatal comorbidity, birth weight, socioeconomic deprivation, and year of birth

**Table 8. –** Intraventricular hemorrhage and risk of childhood hospitalization in term and preterm infants

| | Term neonates with hemorrhage | | Preterm neonates with hemorrhage | | Preterm neonates without hemorrhage | |
|---|---|---|---|---|---|---|
| | No of infants | Hazard ratio (95% CI)* | No of infants | Hazard ratio (95% CI)* | No of infants | Hazard ratio (95% CI)* |
| Cardiovascular | 21 | 11.69 (7.43-18.41) | 93 | 3.02 (2.32-3.93) | 976 | 1.57 (1.42-1.75) |
| Respiratory | 57 | 2.68 (2.07-3.48) | 451 | 1.94 (1.75-2.16) | 10,228 | 1.49 (1.45-1.53) |
| Metabolic | <5 | 3.28 (0.82-13.22) | 13 | 1.57 (0.84-2.94) | 264 | 1.37 (1.13-1.66) |
| Gastrointestinal | 22 | 4.29 (2.78-6.63) | 241 | 2.27 (1.93-2.65) | 3,235 | 1.58 (1.50-1.67) |
| Genitourinary | 6 | 3.09 (1.39-6.87) | 32 | 1.87 (1.25-2.79) | 719 | 1.28 (1.16-1.42) |
| Central nervous system | 47 | 23.19 (16.91-31.81) | 145 | 4.03 (3.20-5.06) | 1,085 | 1.37 (1.24-1.50) |
| Cerebral Palsy | 7 | 55.64 (25.98-119.2) | 50 | 9.29 (5.30-16.27) | 173 | 2.39 (1.67-3.43) |
| Meningitis | 11 | 38.09 (20.36-71.23) | 16 | 4.81 (2.52-9.20) | 126 | 1.62 (1.27-2.08) |
| Hydrocephalus | 11 | 198.1 (99.49-394.1) | 50 | 57.58 (26.02-127.4) | 52 | 2.45 (1.57-3.82) |
| Other | 25 | 13.62 (9.09-20.42) | 69 | 2.40 (1.77-3.26) | 818 | 1.25 (1.13-1.40) |
| Musculoskeletal | <5 | 5.00 (1.28-19.50) | <5 | 1.37 (0.52-3.60) | 105 | 0.91 (0.68-1.21) |
| Ophthalmologic | 16 | 9.59 (5.84-15.75) | 75 | 3.40 (2.55-4.55) | 839 | 1.39 (1.25-.155) |
| Otologic | 43 | 1.83 (1.35-2.47) | 285 | 1.35 (1.19-1.53) | 8,680 | 1.22 (1.19-1.26) |
| Infection | 6 | 1.42 (0.64-3.15) | 74 | 1.81 (1.39-2.35) | 1612 | 1.19 (1.11-1.27) |
| Cancer | <5 | 10.25 (3.25-32.30) | 6 | 3.57 (1.24-10.22) | 83 | 0.94 (0.72-1.23) |
| Surgery | 79 | 2.62 (2.05-3.33) | 544 | 1.75 (1.57-1.94) | 13,467 | 1.19 (1.16-1.22) |
| Any | 118 | 3.19 (2.55-4.00) | 768 | 1.82 (1.66-2.00) | 21,172 | 1.30 (1.28-1.33) |

*Hazard ratios are relative to term neonates without hemorrhage, adjusted for maternal age, pregnancy complications, infant sex, neonatal comorbidity, birth weight, socioeconomic deprivation, and year of birth

**Table 9. –** International Classification of Diseases codes for intraventricular hemorrhage and maternal-infant comorbidity

| | International Classification of Diseases 10th Revision |
|---|---|
| Intraventricular hemorrhage | P52.0-P52.3 |
| Grade I | P52.0 |
| Grade II | P52.1 |
| Grade III/IV | P52.2 |
| Neonatal comorbidity | |
| Bronchopulmonary dysplasia | P27.1 |
| Respiratory distress syndrome | P22.0 |
| Necrotizing enterocolitis | P77 |
| Patent ductus arteriosus | Q25.0, P29.3 |
| Sepsis | J95.88, P35, P36, P52.1 |
| Retinopathy of prematurity | H35.1 |
| Pregnancy complications | |
| Gestational diabetes | O24.8 |
| Preeclampsia | O11, O13, O14, O15 |
| Placental abruption | O45 |
| Placenta previa | O44 |
| Sepsis | O41.12, O41.13, O75.3 |

**Table 10. –** International Classification of Diseases codes for childhood hospitalization outcomes

| | International Classification of Diseases 10th Revision |
|---|---|
| Cardiovascular | |
| Acute rheumatic fever | I00-I01 |
| Primary pulmonary hypertension | I27.0 |
| Pericarditis, endocarditis, myocarditis | I30, I32, I33, I39, I40, I41 |
| Cardiomyopathy | I42, I43 |
| Other cardiovascular and conduction disorders | I44-I49 |
| Supraventricular/ventricular tachycardia | I47.1, I47.2 |
| Atrial fibrillation | I48.0 |
| Heart failure | I50 |
| Atherosclerosis | I70 |
| Hypotension | I95 |
| Cardiac murmurs | R01 |
| Respiratory | |
| Acute upper respiratory infections | J0 |
| Influenza and pneumonia | J1 |
| Respiratory syncytial virus | B97.4, J12.1, J20.5, J21.0 |
| Other acute lower respiratory infections | J2 |
| Asthma | J45 |
| Pneumonitis due to solids and liquids | J69.0 |
| Metabolic | |
| Diabetes mellitus | E10-E14 |
| Malnutrition | E40-E46 |
| Obesity | E65, E66 |
| Gastrointestinal | |
| Esophagus, stomach, duodenal disorders | K20-K31 |
| Non-infective enteritis and colitis | K50-K52 |
| Acute appendicitis | K35 |
| Umbilical hernia | K42 |
| Hepatic failure and liver disease | K71-K72 |
| Acute pancreatitis | K85 |
| Abdominal and pelvic pain | R10 |
| Genitourinary | |
| Nephritis | N10-N12 |
| Renal failure | N17-N19 |
| Central nervous system | |
| Cerebral palsy | G80 |
| Meningitis | G00-G03 |
| Hydrocephalus | G91 |
| Other disorders | G12, G40, G41, G47.30 |
| Musculoskeletal | |
| Arthritis | M05-M09 |
| Scoliosis | M41 |
| Systemic connective tissue disorders | M30-M36 |

| | |
|---|---|
| Ophthalmologic | |
| Strabismus | H49-H50 |
| Ptosis of eyelid | H02.4 |
| Lacrimal stenosis | H04.5 |
| Retinal detachments and breaks | H33 |
| Disorders of optic nerve and visual pathways | H46-H48 |
| Visual impairment including blindness | H54 |
| Otologic | |
| Otitis media | H65, H66, H67 |
| Otalgia and effusion | H92 |
| Infection | |
| Vaccine-preventable infections | B01, A36, A37, A33, B06, A08, B26, B05, A80 |
| Cellulitis | L03 |
| Erythema infectiosum | B08.3 |
| Scarlet fever | A38 |

# Chapter 6

# 6. Discussion

## 6.1 Key findings

In our longitudinal study, with over 4 million person-years of follow-up, a cohort of 1322 infants with IVH were studied. Follow-up extended for up to 12 years and infants with neonatal IVH were found to have higher rates of re-hospitalization compared to those without. A range of outcomes outside the traditional neurodevelopment conditions were observed. Results of our study showed that IVH was associated with a variety of disorders in childhood including cardiovascular, ophthalmologic, CNS and musculoskeletal. Most associations were present regardless of severity. Infants with grades III/IV hemorrhage and term neonates with IVH had the highest rates of hospitalization. Due to our study design, there was a decrease in cumulative incidence as a function of time because infants born towards the end of the study period had less follow-up time. However, IVH remains a severe complication during the neonatal period and this study provides new evidence that these infants are at risk of morbidity beyond neurodevelopmental outcomes. Understanding the spectrum of future disease development can help guide clinical management and positively impact future quality of life.

In the neonatal intensive care unit, IVH is a perplexing morbidity to manage. Cases often implicate end-of-life decision-making, conjointly made by parents and healthcare professionals. Individuals implicated in such decisions are vulnerable to moral distress and face complex ethically challenging choices regarding discontinuation of care (19). End-of-life decision-making is often influenced by the prognosis of other children affected by IVH. However, it is difficult to predict the future quality of life because each child is unique and subjected to different circumstances (3). Parents need to juggle multiple ongoing questions and ethical dilemmas such as wanting to maintain life at any cost, preventing pain and suffering, and face unpredictable future outcomes (19).

In regard to the existing literature, most research has focused on neurodevelopmental sequelae of IVH and many other morbidities are rather poorly understood. Known disorders entail mainly learning limitations, neurosensory impairments and serious debilitating conditions such as cerebral palsy (1,2,9,10,24,79). Despite this extensive literature, associations of IVH to other physiological sequelae remain unknown. Comparable data to our study does not exist, therefore it is difficult to determine whether similar effects would be present in other study populations.

Payne *et al*, investigated a similar concept but in a cohort of 1,472 infants born before 27 weeks of gestation, in the USA. In their study, severe IVH was associated with an increased risk for a subset of impairments observed between 18-22 months of age. Findings of their study revealed a 3.44 times the risk of cerebral palsy, 2.04 the risk of neurodevelopmental impairment, and 3.79 times the risk of abnormal gross motor function for infants affected by IVH compared with no hemorrhage (9). Furthermore, they demonstrated that associations for the above outcomes were not strong for infants with mild grades of IVH. Others studies have suggested similar findings indicating that low grade IVH can lead to similar neurodevelopmental pathways as infants with no hemorrhage or simply result in weak impairments (8–10,85). The spectrum of outcome disorders varies tremendously as a function of severity. For this reason, decisions to withhold or continue life-support frequently revolves around infants with severe IVH, despite the lack of data on other future outcomes (3). Although this study aimed to understand the future outcomes related to IVH, their population was restricted to only extremely preterm infants and it is difficult to compare results.

Kuint *et al* conducted a study, examining a range of physiological outcomes, in a group of preterm infants. Their cohort consisted of 6,385 infants born with VLBW (13,119). The exposed population of infants had multiple comorbidities including IVH (only the severe form). Their study examined the risk of hospitalization for these infants up until 18 years of age. Findings of their study revealed that infants with IVH had a 14-fold greater risk of neurosurgical hospitalizations relative to no IVH (13). Repeat admissions were associated to hydrocephalus, shunts implantations and epileptic disorders. Furthermore, infants with IVH had a 2-fold greater risk of hospitalization compared to infants with no hemorrhage. These results were consistent with findings from the study by Payne *et al*. In addition to neurosurgical needs, severe IVH was also associated with the risk of orthopedic and ophthalmologic hospitalization. Although, the latter findings from *Kuint et al* is consistent with the results from our study, they may not generalize to all infants with IVH. Lack of generalization from their study stems from the restricted population of infants weighing $\leq$1,500 grams at birth and having only assessed infants of grade III/IV hemorrhage. Furthermore, outcomes of their study were only categorized by hospital inpatient departments and differed from the classification style of our study.

In our study, we were able to capture the exposure by severity and timing. Both preterm and term IVH were positively associated with increased risk of childhood hospitalization. Since data on term infants is relatively rare, it was interesting to observe a comparison of risks amongst preterm and term infants

within the same cohort. In preterm infants, the pathophysiology of IVH relates to the vascular immaturity of the subependymal germinal matrix where neuronal and glial precursor cells are found (24). Vessel rupture and subsequent hemorrhaging is more likely due to the fragility of the microvasculature. Injury to this region, especially at low gestational ages, can impact neuronal cell maturation and migration to cerebral cortical regions. Cortical regions are important areas of the brain that contain higher levels of functioning related to cognitive, sensory and motor pathways (8,12). In term infants, IVH is primarily due to bleeding from the choroid plexus, an area responsible for the production of CSF. Hemorrhaging in term infants is rare and often secondary to traumatic delivery or birth asphyxia. A small fraction of cases are due to developmental and anatomical anomalies. Therefore, mechanisms causing IVH in term infants might be linked to other genetic or developmental underlying conditions. In our data, term hemorrhage was strongly associated with childhood hospitalization, increasingly more than preterm infants with hemorrhage. Results of this nature might suggest that neurological injury may be more detrimental in term infants, as a great deal of developmental maturation has already occurred and brain spasticity might differ at later gestational ages (12,15,34). Term infants with mild IVH do not necessarily exhibit clinical manifestations resulting in asymptomatic features and may stay undiagnosed. Due to this reality, the incidence of term infants with IVH may be misrepresentative and mainly encompass severe symptomatic cases. Nevertheless, we could not rule out the possibility of unmeasured confounders, which may have inadvertently attenuated the association of preterm hemorrhage with future outcomes. Early death of preterm infants with IVH can affect the association as they do not contribute to future hospitalization.

Infants affected by IVH are vulnerable to a large spectrum of childhood disorders which may be associated to their clinical course of hospitalization as newborns. Neonates with hemorrhaging may simultaneously have other neonatal complications. Common complications include BPD, ROP and NEC, which can increase medical vulnerability (23). It is seen that children with chronic lung disease experience impaired pulmonary function and may require long-term respiratory support whether in the hospital or at home. Ventilator support can include oxygen administration through low-flow nasal cannula, continuous positive airways pressure or endotracheal intubation (15). Pathological conditions of the respiratory system can induce a change at the cellular level. Abnormal cell growth known as cellular dysplasia can increase risk of respiratory infections (120). Extended respiratory support can cause palatal asymmetry and in conjunction with delayed enteral feeding can lead to gastrointestinal problems in infancy (121,122). Prolonged oxygenation can have detrimental effects on visual functioning. ROP is an ophthalmologic condition commonly arising in the neonatal period associated to strabismus and blindness (60). NEC is a

severe gastrointestinal disorder associated with feeding troubles and short bowel syndrome. It often necessitates surgical interventions, early in life, if disease progression reaches intestinal perforation (123). Nearly 30% of short bowel syndrome cases are attributed to surgical resection of the intestines secondary to severe NEC (124). Lastly, post-hemorrhagic hydrocephalus is a severe complication of IVH and can require neurosurgical implantation of a ventriculoperitoneal shunt. The shunt is typically localized in the subdural area of the brain and drains excess fluid to minimize intracranial pressure (125,126). Shunt implantation augments susceptibility for infections rendering infants at high risk for the development of long-term neurocognitive deficits (31,85).

In neonates, the immune system can be immature making them susceptible to infections. In preterm infants, immune immaturity arises from lower levels of immunological cells, a slower immune response and less maternal-fetal antibody transfer (12,57,58). Despite these abnormalities, the body's natural response to injury still causes activation of the sympathetic nervous system and hypothalamic-pituitary-adrenal axis. These pathways allow release of corticosteroids and neurotransmitters; cortisol and catecholamine respectively (127,128). Acute stress induced by cortisol works synergistically with the immune system to fight infection and induce a "fight or flight" response (16). Pro-inflammatory cytokines are also released in response to tissue injury (or hemorrhaging in our case) in order to attract the necessary cells to the affected region (127,129). Cytokines such as interleukins and tumor necrosis factor alpha are necessary for the migration of immune cells which promote tissue repair. However, an influx of immune cells can, inadvertently, damage neuronal structures by overwhelming healthy undamaged surrounding tissue (127,130). In severe cases of hemorrhaging, immunosuppression can ensue resulting in increased susceptibility to infection (128). These early fluctuations have the potential to impact several physiological systems and the propensity for long-term morbidity.

Although this study adjusted for these neonatal comorbidities, it is difficult to eliminate the possibility that these comorbidities influence risk of future disorders. In all, it is evident that IVH may itself lead to morbidity through multifactorial mechanisms (127,128). Overall, these children are medically complex and difficult to manage with prolonged inpatient stay during the neonatal period (131). Anticipating the future health needs of infants with IVH can help improve care coordination and provide families with adequate support.

## 6.2 Strengths and limitations

*Strengths*

Little to no studies exist that have examined the association of IVH to various other physiological systems of the body. This project had a novel outlook and aimed to explore a wide range of morbidities beyond the traditional neurodevelopmental outcomes. With our findings, we can start to understand the extent of disease progression caused by IVH. This further helps expand our scope practice and in return improves our medical practices.

Unlike other studies, this project depicted the exposure in three distinct ways: a binary exposure and through an expression of timing and severity. This design added a bonus perspective that allowed to visualize the effects of IVH via different groupings of gestational age and birthweight in the same study. Having retrieved data retrospectively, this study was able to capture more cases of term infants with IVH, which is otherwise rare. There exists a relatively small pool of research on term infants with IVH and our study was able to conduct side-by-side comparison of risk amongst preterm and term infants, whilst adjusting for the same covariates.

Time-wise, this study covers an extended follow-up period that goes beyond infancy and early infant developmental phases. Foreseeing long-term outcomes enables better understanding of disease progression. Long-term monitoring allowed to have a more realistic determination of future prognosis and discussions pertaining to the expected quality of life of children. At older ages, children can start to express themselves and, in hindsight, remark on their own perceived health. Valuable insight promotes self-reflection, resilience and fuels better decision making.

*Limitations*

Confounding is a problem in epidemiological studies. Confounding bias originates when a variable is independently associated to the exposure and to the outcome (132). This study had some limitations that should be considered regarding confounding. This study was based on hospital discharge abstracts, limited data on several potential confounders, such as ethnicity and maternal smoking were not available. Residual confounding may exist if potential confounders were not thoroughly identified and defined during the conceptualization and analysis phase of the study. Multiple neonatal comorbidities were controlled during the analysis; however, we cannot exclude the possibility of confounding. Other comorbidities, to a less extent might affect the association.

Information bias can occur when the number of exposed or outcomes cases are incorrect, leading to misclassification of subjects (132). It is important to understand that the severity of IVH can change throughout the course of an infant's hospitalization. Inappropriate medical archiving can cause exposure misclassification. Therefore, we cannot exclude the possibility of non-differential misclassification bias due to errors in coding and archiving. Non-differential classification bias may have attenuated associations, although rigorous algorithms are used to validate Quebec hospital data (90).

Generalizability infers the notion of representativeness or applicability to other populations beyond the study cohort (132). This study only accounted for childhood disorders that required hospitalization. Generalizability of infants with IVH to childhood morbidity that do not necessitate inpatient admissions remains to be determined. Some mild conditions could have been monitored from outpatient settings or ambulatory clinics, therefore hospitalization was not always warranted. Neurodevelopment disorders do not regularly require hospitalization and can be treated in non-tertiary institutions, but we did not have information on neurodevelopmental outcomes pertaining to learning delays and child developmental milestones. Overall, despite this limitation, our study does generalize to the entire population of Quebec.

Sample sizes are important and can affect the interpretation of results. In our study, some outcomes including cancer, musculoskeletal, and metabolic disorders were rare. Rarity can lead to smaller sample sizes. With very little number of infants in certain outcome groups, the risk can be drastically skewed by a select few infants. Associations for rare exposures and small sample sizes ought to be interpreted with caution.

Selection bias, which may be a source of problem for our results and can reduce the internal validity of our study. Since the exposure and outcome have already occurred in this retrospective cohort study, a selection bias is unlikely to occur in our study and infants were selected from a large cohort without prior knowledge of their re-hospitalization status. Through nonparticipation of individuals, it is possible that infants who were censored due to loss of follow-up or missing medical insurance numbers could have developed the event. This would can lead to an incorrect estimation of the association, but this information remains unknown.

## 6.3 Clinical and public health implications

As a healthcare professional, my work entails the stabilization of infants in the neonatal intensive care unit. I have first-hand experience working alongside cases of infants diagnosed with IVH. Medical teams associated with caring for sick children are extensive and often the pursuit for continuation of care is based on hope and comparison to other surviving children. There is a great need to develop a consensus on the way in which high risk IVH cases are dealt with and to revise the protocols on better decision making. A large amount of medical resources are utilized throughout the short and long-term management of affected children. As our medical understanding increases, we can help support ourselves and families. Even though IVH is a rare condition and primarily seen in preterm infants, for the small amount of families it does affect, their lives are completely changed. This condition affects multi-organ systems and necessitates a vast network of healthcare professionals working together on a long-term basis. Preventative measures such as awareness and information availability to mothers prenatally can help reduced some risk factors which encompass public health strategies. Especially in today's society where the average maternal age is higher and the use of ART is more prominent, discussion about severe neonatal complications ought to be addressed more in-depth. Major neonatal complications should to be discussed on a similar level as other conditions such as Trisomy 21 (Down syndrome) for example. The idea is to bring forth the importance of their severity and truly help families understand the difficult psychological, emotional and physical journey ahead. Habitually, infants with IVH are extremely sick and at times necessitate end-of-life decision-making (133). Decisions are not easy to make, days if not weeks can pass before a consensual choice is achieved. This prolonged period of uncertainty and worry places a strain on healthcare professionals and families. There is a lot of gray area, often with no clear guidelines regarding withdrawal of care. Findings of this study can help guide resource allocation and improve clinical practice through better comprehension of future medical needs. Hospital protocols need to be continuously revised to meet the standard of care for upcoming populations of low gestational age infants (134). It is evident that a need for institutional change is necessary as this issue impacts the population on a public health scale.

## 6.4 Directions for future research

For years, IVH has been a serious condition that has mainly been studied for its impact on neurodevelopmental outcomes. The current clinical practices and knowledge need further exploration. Research is starting to evaluate a range childhood morbidities amongst the population of extremely premature infants, but studies isolating IVH remain under evaluated. If associations with multi-organ

systems are true, future studies should be repeated with a larger population of infants to validate findings. Once we can get a better understanding of which psychological systems are mainly affected, then causality can be probed further. Lastly, a higher involvement with psychosocial studies can perhaps positively complement epidemiological findings due to a large ethical involvement. The conjoined insight of both qualitative and quantitative results can create a more in depth and holistic comprehension of IVH.

As we know genetic, immunological and cellular pathways are heavily involved with the progression and development of IVH. Examining the epigenetic and genetic features of IVH during prenatal checkups can help better anticipate and potentially reduce the risk of IVH. Extra prenatal testing or screening can help us understand the genetic contributions to the development of IVH. Since several known risk factors already exist and we should start introducing preventive measures and implemental better protocols in hospitals to prevent the onset or progression of IVH.

# Bibliographic References


1. Mukerji A, Shah V, Shah PS. Periventricular/Intraventricular Hemorrhage and Neurodevelopmental Outcomes: A Meta-analysis. Pediatrics. 2015;136(6):1132–43.

2. Volpe JJ. Intracranial Hemorrhage: Subdural, Subarachnoid, Intraventricular (Term Infant). In: Volpe's Neurology of the Newborn. Elsevier; 2018. p. 593–622.

3. Brecht M, Wilkinson DJC. The outcome of treatment limitation discussions in newborns with brain injury. Arch Dis Child - Fetal Neonatal Ed. 2015;100(2):155–60.

4. Papile LA, Burstein J, Burstein R, Koffler H. Incidence and evolution of subependymal and intraventricular hemorrhage: a study of infants with birth weights less than 1,500 grams. J Pediatr. 1978;92(4):529–34.

5. Ballabh P. Intraventricular hemorrhage in premature infants: mechanism of disease. Pediatr Res. 2010;67(1):1–8.

6. Auger N, Quach C, Healy-Profitos J, Lowe AM, Arbour L. Congenital microcephaly in Quebec: baseline prevalence, risk factors and outcomes in a large cohort of neonates. Arch Child Fetal Neonatal Ed. 2018;103(2):F167-f172.

7. Poryo M, Boeckh JC, Gortner L, Zemlin M, Duppre P, Ebrahimi-Fakhari D, et al. Ante-, peri- and postnatal factors associated with intraventricular hemorrhage in very premature infants. Early Hum Dev. 2018;116:1–8.

8. Bolisetty S, Dhawan A, Abdel-Latif M, Bajuk B, Stack J, Lui K. Intraventricular hemorrhage and neurodevelopmental outcomes in extreme preterm infants. Pediatrics. 2014;133(1):55–62.

9. Payne AH, Hintz SR, Hibbs AM, Walsh MC, Vohr BR, Bann CM, et al. Neurodevelopmental outcomes of extremely low-gestational-age neonates with low-grade periventricular-intraventricular hemorrhage. JAMA Pediatr. 2013;167(5):451–9.

10. Patra K, Wilson-Costello D, Taylor HG, Mercuri-Minich N, Hack M. Grades I-II intraventricular hemorrhage in extremely low birth weight infants: effects on neurodevelopment. J Pediatr. 2006;149(2):169–73.

11. van de Bor M, den Ouden L. School performance in adolescents with and without periventricular-intraventricular hemorrhage in the neonatal period. Semin Perinatol. 2004;28(4):295–303.

12. Avery GB, MacDonald MG, Seshia MMK. Avery's neonatology : pathophysiology & management of the newborn. 2016;

13. Kuint J, Lerner-Geva L, Chodick G, Boyko V, Shalev V, Reichman B, et al. Type of Re-Hospitalization and Association with Neonatal Morbidities in Infants of Very Low Birth Weight. Neonatology. 2019;115(4):292–300.

14. Ballabh P. Pathogenesis and prevention of intraventricular hemorrhage. Clin Perinatol. 2014;41(1):47–67.

15. Gomella TL, Cunningham MD, Eyal FG. Neonatology : management, procedures, on-call problems, diseases, and drugs. Seventh edition. New York: McGraw-Hill Education Medical; 2013.

16. Widmaier EP. Vander's human physiology : the mechanisms of body function. Boston: McGraw-Hill Higher Education; 2008.

17. Singh D, Rana K, Mathai S. Role of prophylactic surfactant in preterm infants. Med J Armed Forces India. 2011;67(2):138–41.

18. Sarkar S, Bhagat I, Dechert R, Schumacher RE, Donn SM. Severe intraventricular hemorrhage in preterm infants: comparison of risk factors and short-term neonatal morbidities between grade 3 and grade 4 intraventricular hemorrhage. Am J Perinatol. 2009;26(6):419–24.

19. Kelly J, Welch E. Ethical decision-making regarding infant viability. Nurs Ethics. 2018;25(7):897–905.

20. Coskun Y, Isik S, Bayram T, Urgun K, Sakarya S, Akman I. A clinical scoring system to predict the development of intraventricular hemorrhage (IVH) in premature infants. Childs Nerv Syst. 2018;34(1):129–36.

21. Bolt RJ, Weissenbruch MM van, Lafeber HN, Waal HAD de. Glucocorticoids and lung development in the fetus and preterm infant. Pediatr Pulmonol. 2001;32(1):76–91.

22. Burri PH. Fetal and postnatal development of the lung. Annu Rev Physiol. 1984;46:617–28.

23. Linder N, Haskin O, Levit O, Klinger G, Prince T, Naor N, et al. Risk factors for intraventricular hemorrhage in very low birth weight premature infants: a retrospective case-control study. Pediatrics. 2003;111(5):590–5.

24. Boxwell G. Neonatal Intensive Care Nursing [Internet]. Routledge; 2000 [cited 2019 Feb 17]. Available from: http://ebookcentral.proquest.com/lib/mcgill/detail.action?docID=168469

25. Yoder BA, Albertine KH, Null DM. High-frequency ventilation for non-invasive respiratory support of neonates. Semin Fetal Neonatal Med. 2016;21(3):162–73.

26. McCrea HJ, Ment LR. The diagnosis, management, and postnatal prevention of intraventricular hemorrhage in the preterm neonate. Clin Perinatol. 2008;35(4):777–92.

27. Mitsiakos G, Papathanasiou A-E, Kyriakidis I, Karagianni P, Tsepis K, Tzimou I, et al. Intraventricular Hemorrhage and Platelet Indices in Extremely Premature Neonates. J Pediatr Hematol Oncol. 2016;38(7):533–8.

28. Girelli G, Antoncecchi S, Casadei AM, Del Vecchio A, Isernia P, Motta M, et al. Recommendations for transfusion therapy in neonatology. Blood Transfus. 2015;13(3):484–97.

29. Howarth C, Banerjee J, Aladangady N. Red Blood Cell Transfusion in Preterm Infants: Current Evidence and Controversies. Neonatology. 2018;114(1):7–16.

30. Ibrahim CPH. Hypotension in preterm infants. Indian Pediatr. 2008;45(4):285–94.

31. Brouwer AJ, Groenendaal F, Benders MJ, de Vries LS. Early and late complications of germinal matrix-intraventricular haemorrhage in the preterm infant: what is new? Neonatology. 2014;106(4):296–303.

32. Korobkin R. The relationship between head circumference and the development of communicating hydrocephalus in infants following intraventricular hemmorrhage. Pediatrics. 1975;56(1):74–7.

33. Dineen R, Jaspan T. Clinical Ultrasound -The neonatal brain. In: Allan PL, Baxter GM, Weston MJ, editors. Edinburgh: Churchill Livingstone; 2011. p. 1253–93.

34. Scher MS, Wright FS, Lockman LA, Thompson TR. Intraventricular Hemorrhage in the Full-term Neonate. Arch Neurol. 1982;39(12):769–72.

35. Johnston KM, Gooch K, Korol E, Vo P, Eyawo O, Bradt P, et al. The economic burden of prematurity in Canada. BMC Pediatr. 2014;14:93.

36. Ment LR, Ådén U, Lin A, Kwon SH, Choi M, Hallman M, et al. Gene-environment interactions in severe intraventricular hemorrhage of preterm neonates. Pediatr Res. 2014;75(0):241–50.

37. World Health Organization. New global estimates on preterm birth published [Internet]. [cited 2019 May 7]. Available from: http://www.who.int/reproductivehealth/global-estimates-preterm-birth/en/

38. Glass HC, Costarino AT, Stayer SA, Brett C, Cladis F, Davis PJ. Outcomes for Extremely Premature Infants. Anesth Analg. 2015;120(6):1337–51.

39. Government of Canada. Live births in Canada in 2015 and 2016 [Internet]. Statistics Canada. 2018 [cited 2019 Mar 6]. Available from: https://www150.statcan.gc.ca/n1/daily-quotidien/180430/dq180430f-eng.htm

40. Radic JA, Vincer M, McNeely PD. Outcomes of intraventricular hemorrhage and posthemorrhagic hydrocephalus in a population-based cohort of very preterm infants born to residents of Nova Scotia from 1993 to 2010. J Neurosurg Pediatr. 2015;15(6):580–8.

41. Fumagalli M, Ramenghi LA, De Carli A, Bassi L, Farè P, Dessimone F, et al. Cranial ultrasound findings in late preterm infants and correlation with perinatal risk factors. Ital J Pediatr [Internet]. 2015 Sep 24 [cited 2019 Nov 10];41. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4581101/

42. Blanc AK, Wardlaw T. Monitoring low birth weight: an evaluation of international estimates and an updated estimation procedure. Bull World Health Organ. 2005;12.

43. Cutland CL, Lackritz EM, Mallett-Moore T, Bardají A, Chandrasekaran R, Lahariya C, et al. Low birth weight: Case definition & guidelines for data collection, analysis, and presentation of maternal immunization safety data. Vaccine. 2017;35(48):6492–500.

44. Wardlaw TM, World Health Organization, UNICEF, editors. Low birthweight: country, regional and global estimates. Geneva: WHO ; UNICEF; 2004. 27 p.

45. Mancini MC, Barbosa NE, Banwart D, Silveira S, Guerpelli JL, Leone CR. Intraventricular hemorrhage in very low birth weight infants: associated risk factors and outcome in the neonatal period. Rev Hosp Clin. 1999;54(5):151–4.

46. Gunes SO, Metin Mahmutoglu A, Agarwal A. Genetic and epigenetic effects in sex determination. Birth Defects Res Part C Embryo Today Rev. 2016;108(4):321–36.

47. Ingemarsson I. Gender aspects of preterm birth. BJOG Int J Obstet Gynaecol. 2003;110(20):34–8.

48. Battarbee AN, Glover AV, Vladutiu CJ, Gyamfi-Bannerman C, Aliaga S, Manuck TA, et al. Sex-Specific Differences in Late Preterm Neonatal Outcomes. Am J Perinatol. 2019;

49. Zhao D, Zou L, Lei X, Zhang Y. Gender Differences in Infant Mortality and Neonatal Morbidity in Mixed-Gender Twins. Sci Rep. 2017;7.

50. Government of Canada. Preterm live births in Canada, 2000 to 2013 [Internet]. Statistics Canada. [cited 2019 Aug 17]. Available from: https://www150.statcan.gc.ca/n1/pub/82-625-x/2016001/article/14675-eng.htm

51. Varga P, Berecz B, Pete B, Kollár T, Magyar Z, Jeager J, et al. Trends in Mortality and Morbidity in Infants Under 500 Grams Birthweight: Observations from Our Neonatal Intensive Care Unit (NICU). Med Sci Monit Int Med J Exp Clin Res. 2018;24:4474–80.

52. Manuck TA, RICE MM, BAILIT JL, GROBMAN WA, REDDY UM, WAPNER RJ, et al. Preterm Neonatal Morbidity and Mortality by Gestational Age: A Contemporary Cohort. Am J Obstet Gynecol. 2016;215(1):103e1–14.

53. Lehenbauer DG, Fraser CD 3rd, Crawford TC, Hibino N, Aucott S, Grimm JC, et al. Surgical Closure of Patent Ductus Arteriosus in Premature Neonates Weighing Less Than 1,000 grams: Contemporary Outcomes. World J Pediatr Congenit Heart Surg. 2018;9(4):419–23.

54. Landry JS, Chan T, Lands L, Menzies D. Long-term impact of bronchopulmonary dysplasia on pulmonary function. Can Respir J. 2011;18(5):265–70.

55. Quasney MW, Lopez-Fernandez YM, Santschi M, Watson RS. The outcomes of children with pediatric acute respiratory distress syndrome: proceedings from the Pediatric Acute Lung Injury Consensus Conference. Pediatr Crit Care Med. 2015;16(5):S118-31.

56. Kim KR, Jung SW, Kim DW. Risk factors associated with germinal matrix-intraventricular hemorrhage in preterm neonates. J Korean Neurosurg Soc. 2014;56(4):334–7.

57. Melville JM, Moss TJM. The immune consequences of preterm birth. Front Neurosci. 2013;7.

58. Comim CM, Bussmann RM, Simao SR, Ventura L, Freiberger V, Patricio JJ, et al. Experimental Neonatal Sepsis Causes Long-Term Cognitive Impairment. Mol Neurobiol. 2016;53(9):5928–34.

59. Stey A, Barnert ES, Tseng CH, Keeler E, Needleman J, Leng M, et al. Outcomes and costs of surgical treatments of necrotizing enterocolitis. Pediatrics. 2015;135(5):e1190-7.

60. Page JM, Schneeweiss S, Whyte HE, Harvey P. Ocular sequelae in premature infants. Pediatrics. 1993;92(6):787–90.

61. Watts P, Adams GG, Thomas RM, Bunce C. Intraventricular haemorrhage and stage 3 retinopathy of prematurity. Br J Ophthalmol. 2000;84(6):596–9.

62. Fuchs F, Monet B, Ducruet T, Chaillet N, Audibert F. Effect of maternal age on the risk of preterm birth: A large cohort study. PLoS One [Internet]. 2018 [cited 2019 Apr 16];13(1). Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5791955/

63. Cimadomo D, Fabozzi G, Vaiarelli A, Ubaldi N, Ubaldi FM, Rienzi L. Impact of Maternal Age on Oocyte and Embryo Competence. Front Endocrinol [Internet]. 2018 [cited 2019 Jun 19];9. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6033961/

64. Zenitani M, Sasaki T, Tanaka N, Oue T. Umbilical appearance and patient/parent satisfaction over 5years of follow-up after umbilical hernia repair in children. J Pediatr Surg. 2018 Jul;53(7):1288–94.

65. Sohn K. The trend in the relationship of advanced maternal age to preterm birth and low birthweight. Eur J Contracept Reprod Health Care Off J Eur Soc Contracept. 2017;22(5):363–8.

66. Whitehead NS. The relationship of socioeconomic status to preterm contractions and preterm delivery. Matern Child Health J. 2012;16(8):1645–56.

67. Morrison J, Najman JM, Williams GM, Keeping JD, Andersen MJ. Socio-economic status and pregnancy outcome. An Australian study. Br J Obstet Gynaecol. 1989;96(3):298–307.

68. Matijasevich A, Victora CG, Lawlor DA, Golding J, Menezes AMB, Araújo CL, et al. Association of socioeconomic position with maternal pregnancy and infant health outcomes in birth cohort studies from Brazil and the UK. J Epidemiol Community Health. 2012;66(2):127–35.

69. Bushnik T, Yang S, Kaufman JS, Kramer MS, Wilkins R. Socioeconomic disparities in small-for-gestational-age birth and preterm birth. Health Rep. 2017;28(11):3–10.

70. Hartley D. Rural Health Disparities, Population Health, and Rural Culture. Am J Public Health. 2004;94(10):1675–8.

71. Abdel-Latif ME, Bajuk B, Oei J, Vincent T, Sutton L, Lui K. Does rural or urban residence make a difference to neonatal outcome in premature birth? A regional study in Australia. Arch Dis Child Fetal Neonatal Ed. 2006;91(4):F251–6.

72. Van Way CW. Is There a Surgeon Shortage? Mo Med. 2010;107(5):309–12.

73. Norwitz ER, Arulkumaran S, Fowlie A, Symonds I. Oxford American Handbook of Obstetrics and Gynecology. Cary, United States: Oxford University Press USA - OSO; 2007.

74. Kilpatrick SJ, Abreo A, Gould J, Greene N, Main EK. Confirmed severe maternal morbidity is associated with high rate of preterm delivery. Am J Obstet Gynecol. 2016;215(2):233.e1-7.

75. Han RH, McKinnon A, CreveCoeur TS, Baksh BS, Mathur AM, Smyser CD, et al. Predictors of mortality for preterm infants with intraventricular hemorrhage: a population-based study. Childs Nerv Syst ChNS Off J Int Soc Pediatr Neurosurg. 2018;

76. Gibbs RS, Karlan BY, Haney AF, Nygaard IE. Danforth's Obstetrics and Gynecology. Philadelphia: Wolters Kluwer; 2008.

77. Intapad S, Alexander BT. Pregnancy Complications and Later Development of Hypertension. Curr Cardiovasc Risk Rep. 2013;7(3):183–9.

78. Tepper NK, Farr SL, Cohen BB, Nannini A, Zhang Z, Anderson JE, et al. Singleton preterm birth: risk factors and association with assisted reproductive technology. Matern Child Health J. 2012;16(4):807–13.

79. Calisici E, Eras Z, Oncel MY, Oguz SS, Gokce İK, Dilmen U. Neurodevelopmental outcomes of premature infants with severe intraventricular hemorrhage. J Matern-Fetal Neonatal Med Off J Eur Assoc Perinat Med Fed Asia Ocean Perinat Soc Int Soc Perinat Obstet. 2015;28(17):2115–20.

80. Ralph MAL, Jefferies E, Patterson K, Rogers TT. The neural and computational bases of semantic cognition. Nat Rev Neurosci. 2017;18(1):42–55.

81. Armstrong KH, Agazzi HC. The Bayley-III Cognitive Scale. In: Weiss LG, Oakland T, Aylward GP, editors. Bayley-III Clinical Use and Interpretation [Internet]. San Diego: Academic Press; 2010 [cited 2019 Jun 22]. p. 29–45. (Practical Resources for the Mental Health Professional). Available from: http://www.sciencedirect.com/science/article/pii/B9780123741776100029

82. Lowe JR, Erickson SJ, Schrader R, Duncan AF. Comparison of the Bayley II Mental Developmental Index and the Bayley III Cognitive Scale: Are we measuring the same thing? Acta Paediatr Oslo Nor 1992. 2012;101(2):e55–8.

83. Rapp B, Wiley RW. Re-learning and remembering in the lesioned brain. Neuropsychologia. 2019 Jun 18;107126.

84. Futagi Y, Toribe Y, Ogawa K, Suzuki Y. Neurodevelopmental outcome in children with intraventricular hemorrhage. Pediatr Neurol. 2006;34(3):219–24.

85. Reubsaet P, Brouwer AJ, van Haastert IC, Brouwer MJ, Koopman C, Groenendaal F, et al. The Impact of Low-Grade Germinal Matrix-Intraventricular Hemorrhage on Neurodevelopmental Outcome of Very Preterm Infants. Neonatology. 2017;112(3):203–10.

86. Nelson KB, Ellenberg JH. Neonatal signs as predictors of cerebral palsy. Pediatrics. 1979;64(2):225–32.

87. World Health Organization. WHO | International Classification of Functioning, Disability and Health (ICF). WHO.

88. Ronen GM, Fayed N, Rosenbaum PL. Outcomes in pediatric neurology: a review of conceptual issues and recommendationsThe 2010 Ronnie Mac Keith Lecture. Dev Med Child Neurol. 2011;53(4):305–12.

89. Institut national de santé publique du Québec. Portrait de santé du Québec et de ses régions 2006 : les statistiques - Deuxième rapport national sur l'état de santé de la population du Québec. INSPQ.

90. Ministry of Health and Social Services. Med-Echo System Normative Framework-Maintenance and use of data for the study of hospital clientele. Gov Quebec. 2017;

91. Alexander GR, Himes JH, Kaufman RB, Mor J, Kogan M. A United States National Reference for Fetal Growth. Obstet Gynecol. 1996;87(2):163–8.

92. Centers for Disease Control and Prevention. International Classification of Diseases, tenth Revision. 2019.

93. Landry JS, Croitoru D, Menzies D. Validation of ICD-9 diagnostic codes for bronchopulmonary dysplasia in Quebec's provincial health care databases. Chronic Dis Inj Can. 2012 Dec;33(1):47–52.

94. Steliarova-Foucher E, Stiller C, Lacour B, Kaatsch P. International Classification of Childhood Cancer, third edition. Cancer. 2005;103(7):1457–67.

95. Canadian Institute for Health Information. Canadian Classification of Health Interventions. 2015.

96. Unger SA, Bogaert D. The respiratory microbiome and respiratory infections. J Infect. 2017;74 Suppl 1:S84–8.

97. Homaira N, Oei J-L, Mallitt K-A, Abdel-Latif ME, Hilder L, Bajuk B, et al. High burden of RSV hospitalization in very young children: a data linkage study. Epidemiol Infect. 2016;144(8):1612–21.

98. Boyd K. Back to the Basics: Community-Acquired Pneumonia in Children. Pediatr Ann. 2017;46(7):e257–61.

99. Guilbert TW, Bacharier LB, Fitzpatrick AM. Severe asthma in children. J Allergy Clin Immunol Pract. 2014;2(5):489–500.

100. Kumar V. Influenza in Children. Indian J Pediatr. 2017;84(2):139–43.

101. Kondrich J, Rosenthal M. Influenza in children. Curr Opin Pediatr. 2017;29(3):297–302.

102. Campbell MK. Biological, environmental, and social influences on childhood obesity. Pediatr Res. 2016;79(1–2):205–11.

103. Temneanu OR, Trandafir LM, Purcarea MR. Type 2 diabetes mellitus in children and adolescents: a relatively new clinical problem within pediatric practice. J Med Life. 2016;9(3):235–9.

104. Endris N, Asefa H, Dube L. Prevalence of Malnutrition and Associated Factors among Children in Rural Ethiopia. BioMed Res Int. 2017;2017:6587853.

105. Halle MP, Lapsap CT, Barla E, Fouda H, Djantio H, Moudze BK, et al. Epidemiology and outcomes of children with renal failure in the pediatric ward of a tertiary hospital in Cameroon. BMC Pediatr. 2017;17(1):202.

106. Guignard J-P, Ali US. Acute Renal Failure in the Neonate. J Pediatr Intensive Care. 2016;5(2):42–9.

107. Lewis KA, Brown SA, Tiziani S, Carrasco R. Sociocultural Considerations in Juvenile Arthritis: A Review. J Pediatr Nurs. 2017;37:13–21.

108. Leung AKC, Wong AHC. Acute Otitis Media in Children. Recent Pat Inflamm Allergy Drug Discov. 2017;11(1):32–40.

109. Kong K, Lannigan FJ, Morris PS, Leach AJ, O'Leary SJ. Ear, nose and throat surgery: All you need to know about the surgical approach to the management of middle-ear effusions in Australian Indigenous and non-Indigenous children. J Paediatr Child Health. 2017;53(11):1060–4.

110. Kim SH, Kim TH, Byun JY, Park MS, Yeo SG. Clinical Differences in Types of Otalgia. J Audiol Otol. 2015;19(1):34–8.

111. Public Health Agency of Canada. Vaccine-Preventable Diseases. aem. 2002.

112. Rasquin A, Lorenzo CD, Forbes D, Guiraldes E, Hyams JS, Staiano A, et al. Childhood Functional Gastrointestinal Disorders: Child/Adolescent. Gastroenterology. 2006;130(5):1527–37.

113. Pampalon R, Hamel D, Gamache P, Simpson A, Philibert MD. Validation of a deprivation index for public health: a complex exercise illustrated by the Quebec index. Chronic Inj Can. 2014;34(1):12–22.

114. Austin PC, Fine JP. Practical recommendations for reporting Fine-Gray model analyses for competing risk data. Stat Med. 2017;36(27):4391–400.

115. Kleinbaum DG, Klein M. Survival analysis : a self-learning text. 3rd ed. New York, NY: Springer; 2012.

116. Lin DY, Wei LJ. The Robust Inference for the Cox Proportional Hazards Model. J Am Stat Assoc. 1989;84(408):1074–8.

117. Thabane L, Mbuagbaw L, Zhang S, Samaan Z, Marcucci M, Ye C, et al. A tutorial on sensitivity analyses in clinical trials: the what, why, when and how. BMC Med Res Methodol. 2013;13:92.

118. Anderson JJ. Using the statistical analysis system as an educational audit software system. J Account Educ. 1985;3(1):131–44.

119. Kuint J, Lerner-Geva L, Chodick G, Boyko V, Shalev V, Reichman B, et al. Rehospitalization Through Childhood and Adolescence: Association with Neonatal Morbidities in Infants of Very Low Birth Weight. J Pediatr. 2017;188:135–41.

120. Baraldi E, Filippone M. Chronic Lung Disease after Premature Birth. N Engl J Med. 2007;357(19):1946–55.

121. Macey-Dare LV, Moles DR, Evans RD, Nixon F. Long-term effect of neonatal endotracheal intubation on palatal form and symmetry in 8-11-year-old children. Eur J Orthod. 1999;21(6):703–10.

122. Hawdon JM, Beauregard N, Slattery J, Kennedy G. Identification of neonates at risk of developing feeding problems in infancy. Dev Med Child Neurol. 2000;42(4):235–9.

123. Frost BL, Modi BP, Jaksic T, Caplan MS. New Medical and Surgical Insights Into Neonatal Necrotizing Enterocolitis: A Review. JAMA Pediatr. 2017 01;171(1):83–8.

124. Amin SC, Pappas C, Iyengar H, Maheshwari A. Short Bowel Syndrome in the Nicu. Clin Perinatol. 2013;40(1).

125. Christian EA, Melamed EF, Peck E, Krieger MD, McComb JG. Surgical management of hydrocephalus secondary to intraventricular hemorrhage in the preterm infant. J Neurosurg Pediatr. 2016;17(3):278–84.

126. Kazan S, Güra A, Uçar T, Korkmaz E, Ongun H, Akyuz M. Hydrocephalus after intraventricular hemorrhage in preterm and low-birth weight infants: analysis of associated risk factors for ventriculoperitoneal shunting. Surg Neurol. 2005;64 Suppl 2:S77-81.

127. Zhang J, Shi K, Li Z, Li M, Han Y, Wang L, et al. Organ- and cell-specific immune responses are associated with the outcomes of intracerebral hemorrhage. FASEB J Off Publ Fed Am Soc Exp Biol. 2018;32(1):220–9.

128. Kamel H, Iadecola C. Brain-immune interactions and ischemic stroke: clinical implications. Arch Neurol. 2012;69(5):576–81.

129. Murphy K, Weaver C. Janeway's immunobiology. Biochemistry and Molecular Biology Education; 2017.

130. Szpecht D, Szymankiewicz M, Seremak-Mrozikiewicz A, Gadzinowski J. The role of genetic factors in the pathogenesis of neonatal intraventricular hemorrhage. Folia Neuropathol. 2015;53(1):1–7.

131. Cohen E, Kuo DZ, Agrawal R, Berry JG, Bhagat SKM, Simon TD, et al. Children with medical complexity: an emerging population for clinical and research initiatives. Pediatrics. 2011;127(3):529–38.

132. Gordis L. Epidemiology [Internet]. Philadelphia: Elsevier; 2014 [cited 2019 Jul 15]. Available from: http://ebookcentral.proquest.com/lib/mcgill/detail.action?docID=1429529

133. Sawyer T. Withdrawing Support for Withdrawing Support From Premature Infants With Severe Intracranial Hemorrhage. Pediatrics. 2008;121(5):1071–2.

134. Christ L, Barber J, Murray A, Dunleavy M, Stoller J, Taha D, et al. Reducing Intraventricular Hemorrhage in a Level Iii Neonatal Intensive Care Unit. BMJ Qual Saf. 2015;24(11):731–2.