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Neonatal and Developmental Outcomes of Late Preterm and Early Term Birth

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A thesis submitted in partial fulfillment of the requirements for the degree in Doctor of Philosophy

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(Thesis format: Integrated Article)

by

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Abstract

Research suggests increased risk for adverse outcomes associated with late preterm (34-36 weeks) and early term (37-38 weeks) birth versus full term (39-41 weeks). However, it remains unclear to what extent these outcomes are associated with physiological immaturity or factors leading to or associated with early birth.

The first objective was to elucidate the role of gestational age in determining risk of poor neonatal outcomes in the context of biological determinants of preterm birth. A retrospective cohort study of singletons delivered at 34-41 weeks to London-Middlesex (Canada) mothers was conducted using perinatal and discharge abstract databases (N=38,807, 2002-2011). Modified Poisson regression showed increased risk for NICU triage/admission and respiratory morbidity among infants born late preterm and early term. The effect of gestational age was partially explained by biological determinants (infection and inflammation, placental ischemia and other hypoxia, other [diabetes/hydramnios]) acting through gestational age. Placental ischemia and other hypoxia exacerbated the effect of gestational age on poor outcomes.

The second objective was to elucidate the role of gestational age in determining risk of poor developmental outcomes in the context of proximal social processes. A secondary analysis of singletons delivered at 34-41 weeks was conducted using the National Longitudinal Survey of Children and Youth (N=15,099, 2-3 years; N=12,203, 4-5 years). Modified Poisson regression did not show increased risk for developmental delay or receptive vocabulary delay among children born late preterm or early term. Proximal social processes (parenting interactions, effectiveness, consistency) did not modify the effect of gestational age but were strong predictors of poor outcomes.

The third objective, secondary to central analyses, was to examine associations between biological determinants of preterm birth and gestational age among spontaneous singleton births (perinatal database; N=17,678). Multinomial logistic regression showed associations between these pathological processes and both late preterm and early term birth.

Poor neonatal outcomes among infants born late preterm and early term are due to physiological immaturity and also to biological determinants of preterm birth acting through and with gestational age to produce poor outcomes. Beyond the neonatal period, social factors are the most important influences on development in births close to full term.

Keywords

Late preterm, early term, neonatal morbidity, developmental delay

Co-Authorship Statement

Each of the three manuscripts contained within this thesis is based upon research that was primarily conceived of and designed by the first author, Hilary K. Brown, as a component of her doctoral work completed under the supervisory guidance of Dr. M. Karen Campbell. As well, Hilary K. Brown was primarily responsible for the analyses. The author's supervisor, Dr. M. Karen Campbell, and committee members, Dr. Kathy N. Speechley, Dr. Jennifer Macnab, and Dr. Renato Natale provided ongoing contributions in the form of regular feedback and methodological and statistical advice throughout the course of the research. Hilary K. Brown was the primary author of each manuscript. The above four committee members were co-authors of the manuscripts associated with Chapters Three through Five of the thesis, as indicated in the footnote in the introduction of each of these chapters. The data for this research were obtained from the London Health Sciences Centre perinatal database, of which Dr. Renato Natale is director, and from the Statistics Canada Research Data Centres.

Dedication

This thesis is dedicated to my father, who always asks the creative questions.

I hope to someday be even half the scientist you are.

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List of Abbreviations

aOR	Adjusted odds ratio
aRR	Adjusted relative risk
CIHI	Canadian Institute for Health Information
ECD	Early Childhood Development Cohort
ICD	International Classification of Disease
M	Mean
MSD	Motor and Social Development Scale
NICU	Neonatal intensive care unit
NLSCY	National Longitudinal Survey of Children and Youth
OR	Odds ratio
PAF	Population attributable fraction
PMK	Person most knowledgeable
PPVT-R	Peabody Picture Vocabulary Test-Revised
RERI	Relative excess risk due to interaction
RR	Relative risk
SD	Standard deviation
WHO	World Health Organization

Chapter 1

Introduction

1.1 Background and Overview

Since 1995, the incidence of preterm birth (i.e., delivery at less than 37 weeks gestation) has increased by 17%, and, as of 2004, preterm birth accounted for 8.2% of all births in Canada (1). The risks associated with very preterm birth (at less than 34 weeks) are well-established. However, 75% of preterm births are delivered closer to term, between 34 and 36 weeks (2). Contrary to historical thinking, these births, now labeled "late preterm," may be associated with heightened risks for poor neonatal and developmental outcomes (3-6). Typically, the comparison group for late preterm births has been births at 37 weeks or later (i.e., term births). Technically, a full term gestation lasts until 39 to 41 weeks (2). Early term births, at 37 or 38 weeks, account for 17.5% of live births (7) and may also have increased risk for poor outcomes compared to full term births (8-11).

1.1.1 Overall Aim

Based on existing evidence, it is unclear to what extent these poor outcomes are associated directly with being born early (i.e., physiological immaturity) or with factors leading to or associated with being born early (i.e., biological or social factors). Therefore, the overall aim of this thesis was to elucidate the role that gestational age plays in determining the risk of poor neonatal and developmental outcomes among individuals born late preterm and early term by examining the contribution of gestational age to these outcomes in the context of biological determinants of preterm birth and proximal social processes.

1.1.2 Objectives and Research Questions

The *first objective* of this thesis was to quantify the risk of poor neonatal outcomes among infants born late preterm and early term. This objective was addressed using a retrospective cohort study. Data were obtained from the London Health Sciences Centre (London, Ontario) perinatal and discharge abstract databases. The study population

included singleton births, delivered at 34 to 41 weeks to mothers residing in the City of London or Middlesex County (2002-2011). Research questions were:

1a. *How does the risk of poor neonatal outcomes among infants born late preterm and early term compare to that of infants born full term?* The outcomes that were compared to answer this question were: (a) neonatal intensive care unit triage/admission and (b) respiratory morbidity (i.e., respiratory distress syndrome, transient tachypnea of the newborn, other respiratory distress of the newborn, respiratory distress of the newborn unspecified, bronchopulmonary dysplasia, or persistent pulmonary hypertension).

1b. *What is the inter-relationship between gestational age and the biological determinants of preterm birth in determining the risk of these poor neonatal outcomes?* To address this question, analyses were conducted to determine if: (a) gestational age acts as a partial mediator between the biological determinants of preterm birth and poor neonatal outcomes listed above; and (b) biological determinants of preterm birth modify the effect of gestational age on these outcomes. The biological determinants of preterm birth that were examined included infection and inflammation, placental ischemia and other hypoxia, and other biological determinants (i.e., pre-existing and gestational diabetes mellitus, polyhydramnios, and oligohydramnios).

The *second objective* of this thesis was to quantify the risk of poor developmental outcomes among children born late preterm and early term. This objective was addressed using a secondary analysis of a longitudinal survey. Data were obtained from the National Longitudinal Survey of Children and Youth Early Childhood Developmental Cohorts (Cycles 2 [1996-1997] through 6 [2004-2005]). The study population included singletons, delivered at 34 to 41 weeks. Research questions were:

2a. *How does the risk of poor developmental outcomes among children born late preterm and early term compare to that of children born full term?* The outcomes that were compared to answer this question were: (a) developmental delay (measured by the Motor and Social Development Scale) at 2 to 3 years of age and

(b) receptive vocabulary delay (measured by the Peabody Picture Vocabulary Test-Revised) at 4 to 5 years of age.

2b. *What is the inter-relationship between gestational age and proximal social processes in determining the risk of these poor developmental outcomes?* To address this question, analyses were conducted to determine if proximal social processes modify the effect of gestational age on the developmental outcomes listed above. The proximal social processes that were examined included parenting interactions, parenting effectiveness, and parenting consistency.

The *third objective* of this thesis was to examine the association between the biological determinants of preterm birth and spontaneous birth in the late preterm and early term periods. Although secondary to the central aim of this thesis, this analysis was intended to demonstrate the pathological nature of the mechanisms associated with even non-medically indicated births in the weeks just prior to full term. This objective was addressed using a subsample of births following spontaneous labour, taken from the data source and study population described in the *first objective*. The research question was:

3a. *Do biological determinants of preterm birth, grouped according to common hypothesized pathophysiological mechanisms, contribute to spontaneous early birth of singletons during the late preterm and early term periods?* The biological determinants of preterm birth that were examined included infection and inflammation, placental ischemia and other hypoxia, and other biological determinants of preterm birth (i.e., pre-existing and gestational diabetes mellitus, polyhydramnios, and oligohydramnios).

1.2 Structure of the Thesis

In accordance with The University of Western Ontario's School of Graduate and Postdoctoral Studies' guidelines, the work of this thesis is presented as an integrated article style thesis with a series of three manuscripts. A brief description of these manuscripts is provided below. A complete description of the methodological details of this thesis is provided in several appendices at the end of this document (Appendix A for

Chapter 3 and Chapter 5 [*objective one* and *objective three*, respectively] and Appendix B for Chapter 4 [*objective two*]). Additional appendices are provided for sample size calculations (Appendix C) and statements of ethics approval (Appendix D).

The literature review and conceptual models are presented in Chapter Two. This chapter presents a review of the literature pertaining to late preterm and early term birth along with a critical evaluation of the studies' methodologies. Conceptual models are presented which depict the relationships among gestational age and factors leading to or associated with gestational age (i.e., biological determinants of preterm birth and proximal social processes), as well as their impacts on neonatal and developmental outcomes, in line with the thesis objectives. These conceptual models are the basis for the analyses conducted in Chapters 3 through 5.

Chapter Three includes a manuscript entitled "Neonatal Outcomes of Late Preterm and Early Term Birth: Roles of Gestational Age and Biological Determinants of Preterm Birth." A version of this chapter was published in the *International Journal of Epidemiology*. This chapter addresses the *first objective* of the thesis by examining neonatal outcomes of late preterm and early term birth and the roles of gestational age and the biological determinants of preterm birth in determining the risks of these outcomes.

Chapter Four includes a manuscript entitled "Developmental Outcomes of Late Preterm and Early Term Birth: Roles of Gestational Age and Proximal Social Processes." A version of this chapter was accepted by *Pediatrics*. This chapter addresses the *second objective* of the thesis by examining developmental outcomes of late preterm and early term birth and the roles of gestational age and proximal social processes (i.e., parenting skills) in determining risks of these outcomes.

Chapter Five includes a manuscript entitled "Biological Determinants of Spontaneous Late Preterm and Early Term Birth." A version of this chapter was submitted to the *British Journal of Obstetrics and Gynaecology*. This chapter addresses the *third objective* of the thesis by examining the association between biological determinants of preterm birth and spontaneous late preterm and early term birth.

Chapter Six (Discussion) summarizes the main findings of the thesis and draws connections among the chapters. Overall strengths and limitations of this research as well as implications for clinical practice and directions for future research are discussed.

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Chapter 2

Literature Review

2.1 Introduction

The risks associated with very preterm birth (at less than 34 weeks) are well-established. Traditionally, infants born closer to term were treated as developmentally similar to term infants. However, in 2005, a U.S. National Institute of Child Health and Human Development panel re-defined infants born between 34 and 36 weeks as "late preterm" to emphasize their previously underappreciated vulnerability (1, 2). Subsequent studies have generally confirmed increased risk for poor neonatal and developmental outcomes associated with late preterm birth. Moreover, there is emerging evidence that infants born between 37 and 38 weeks (now called "early term") may also be at increased risk for poor neonatal and developmental outcomes compared to those born full term (39 to 41 weeks). (Refer to Figure 2.1 for a schematic showing these gestational age definitions.)

Despite the influx of research surrounding late preterm and early term birth, it remains unclear to what extent adverse neonatal and developmental outcomes among individuals born late preterm and early term are associated directly with being born early (i.e., physiological immaturity) or with factors leading to or associated with being born early (i.e., biological or social factors). This chapter presents a critical review of the literature regarding neonatal and developmental outcomes of late preterm and early term birth. Based on this review, conceptual models (Figure 2.2 and Figure 2.3) are proposed to elucidate the role of gestational age in the context of biological and social factors which may explain or exacerbate the risk of poor neonatal and developmental outcomes among individuals born late preterm and early term.

Studies included in the literature review were obtained from searches of the Medline and Embase databases and of the reference lists of each of the obtained articles. Studies were excluded that: 1) did not define late preterm and early term birth according to definitions set by the U.S. National Institute of Child Health and Human Development (i.e., 34 to 36 weeks and 37 to 38 weeks, respectively); 2) did not include a reference group (e.g., term

or full term); and 3) did not include a measure of statistical significance (e.g., a p-value or confidence interval).

2.2 Neonatal Outcomes

2.2.1 Neonatal Outcomes of Late Preterm Birth

Studies generally show that infants born late preterm are at increased risk for poor neonatal outcomes as measured by general indicators of newborn health, respiratory morbidity and other specific morbidity, and neonatal mortality. Refer to Table 2.1 for a summary of these studies.

General Indicators of Newborn Health

Studies have uniformly found that infants born late preterm are at increased risk for admission to the neonatal intensive care unit (**NICU**) compared to infants born at term. The strongest evidence for this association comes from several retrospective cohort studies, characterized by large sample sizes, population-based data from administrative datasets or several clinical centres covering both secondary and tertiary levels of care, and analytic control of other potential explanatory factors (hereinafter referred to as "high quality" studies). For example, in a Canadian study of data from the Manitoba Centre for Health Policy, Ruth et al. (3) found that, relative to infants born at 39 to 40 weeks, there was a statistically significant increased risk for NICU admission at each week of gestation within the late preterm period. Similar risks, relative to 37 to 40 weeks, were reported by a large U.S. study of Vital Statistics records, conducted by Cheng et al. (4), in which the sample was limited to singleton births following low risk pregnancies (i.e., with no maternal medical conditions). Several studies with limitations in their study designs found similar results. In a study conducted in Israel, Melamed et al. (5) found increased risk for NICU admission among late preterm births compared to births at 37 to 40 weeks, after controlling for confounders; however, their data were from a single tertiary care centre, increasing the possibility that the observed risk was due not just to prematurity but also to the reasons for birth at a high risk centre. Santos et al. (6) conducted a prospective cohort study of five hospitals in Brazil; interviews of women

shortly after delivery again revealed increased risk for NICU admission following late preterm birth compared to birth at 37 to 41 weeks, after controlling for confounders. However, results may not be generalizable to North America. These findings have been replicated in several smaller studies from single hospital centres in Canada (7), the U.S. (8, 9), and elsewhere (10, 11); these smaller studies did not control for confounders.

Studies have consistently shown that infants born late preterm are at increased risk for longer stay during the birth hospitalization. However, each of these studies was limited in some way, and only two studies controlled for confounders. In their study conducted in Israel, Melamed et al. (5) found increased risk for hospital stay more than 7 days for infants born late preterm; however, their study sample was limited to a single tertiary care centre. Similarly, although Bird et al. (12) also found increased risk for longer stay among U.S. infants born late preterm, they used Kaiser Permanente data which may indicate a low income sample at risk for both early birth and poor neonatal outcomes. A study of a tertiary care centre and its surrounding community hospitals in Switzerland conducted by Leone et al. (13) showed similar results but did not control for confounders. Several smaller studies also with unadjusted estimates found similar results (8, 9, 11).

Studies examining Apgar scores, which measure the need for resuscitation shortly after birth (14), have had more variable findings. Two studies controlled for potential confounders in their analyses. Cheng et al. (4), in their study of U.S. Vital Statistics records of low risk pregnancies, found increased risk for 5-minute Apgar scores less than 7 among infants born late preterm compared to those born at 37 to 40 weeks. Similar results were shown by Santos et al. (6) in their Brazilian prospective cohort study. In contrast, two studies that did not control for confounders failed to find an association with 5-minute Apgar scores less than 4 (8) or less than 7 (13).

Studies have also measured general newborn health by constructing composite outcomes of diagnoses and other indicators; despite different definitions, results have been consistent. This evidence comes from several high quality retrospective cohort studies. In a study of all hospital births in France, Gouyon et al. (15) found that infants born late preterm were at increased risk, compared to infants born at 39 to 41 weeks, for severe

morbidity, defined as death and/or severe neurological condition. Shapiro-Mendoza et al. (16) also found increased risk for a high threshold measure of morbidity (i.e., birth hospitalization stay of more than 5 nights and life-threatening morbidity) when they assessed Massachusetts birth and death certificates. In their Manitoba study, Ruth et al. (3) found increased risk for a low threshold composite of "any diagnosis." These findings have been confirmed in more limited studies, including the studies by Leone et al. (13), which did not control for confounders, and Santos et al. (6), which had a low income sample. Several single centre studies, some of which controlled for confounders (5, 17, 18) and some of which did not (8, 19) also found similar results.

Respiratory Morbidity and Other Specific Diagnoses

Respiratory morbidity is the most common neonatal morbidity among infants born late preterm, and a number of studies have examined this outcome with fairly consistent results. Several high quality retrospective cohort studies provide the most convincing evidence. For example, in a large retrospective cohort study of 12 clinical centres in the U.S., the Consortium on Safe Labour (20) showed increased risk (compared to infants born at 39 to 40 weeks) for respiratory distress syndrome, transient tachypnea of the newborn, pneumonia, respiratory failure, surfactant use, and ventilator use. In their French Study, Gouyon et al. (15) found increased risk for severe respiratory morbidity, defined as respiratory distress treated by mechanical ventilation or continuous positive airway pressure. Similar results were shown by other high quality studies described previously; together, they showed increased risk for respiratory distress syndrome (3), hyaline membrane disease (4), and ventilation use (4). Additional studies found similar results after controlling for confounders but were conducted in single tertiary centres (5, 18, 21), in Medicaid populations (12), or in low income communities (22). Several other studies conducted in Canada (7), the U.S. (8, 9, 17), Europe (10, 13, 23), and elsewhere (11, 19), which did not control for confounders, also found increased risk for neonatal respiratory morbidity among infants born late preterm.

Studies have also shown associations between late preterm birth and other specific neonatal diagnoses. High quality retrospective cohort studies have found increased risk

for hyperbilirubinemia (3) and suspected or confirmed sepsis (4) after controlling for confounders. Similar associations with these outcomes as well as hypoglycemia and temperature instability have been seen in studies that were limited by failure to control for confounders or by utilization of high risk samples (5, 8-13, 17-19, 23). Several studies have also shown increased risk for necrotizing enterocolitis (5, 19, 23), but only one study (which was limited to a single tertiary centre) controlled for confounders (5). An additional study only found increased risk at 34 and 35 weeks (8). Several smaller single centre studies did not find risks for sepsis (10, 17), hypoglycemia (9), temperature instability (17), or necrotizing enterocolitis (17). Fewer studies have examined more severe morbidity such as neurological morbidity. After controlling for confounders, Cheng et al. (4) and Bird et al. (12) found increased risk, respectively, for seizures and apnea. McIntire et al. (8) found an association with intraventricular hemorrhage but did not control for confounders. Several smaller studies did not find associations with neurological morbidity (17, 19, 23).

Neonatal Mortality

Mortality is rare in the late preterm period, and studies have shown conflicting findings over whether there is increased risk for infants born late preterm compared to those born at term. Most of the large U.S. studies of Vital Statistics did not control for confounders. Using data from the National Center for Health Statistics, Reddy et al. (24) found that infants born late preterm were at increased risk for neonatal mortality compared to infants born at 39 to 40 weeks. Young et al. (25) found similar risks for early neonatal and neonatal mortality (compared to births at 40 weeks) in Utah. These findings have been confirmed by additional studies which did control for confounders. In a study of linked live birth-infant death files, Kramer et al. (26) found that Canadian and U.S. infants born late preterm were at increased risk for early and late neonatal mortality. Santos et al. (6) also found increased risk for neonatal mortality relative to 37 to 40 weeks, but their study was conducted in Brazil and had a much higher overall neonatal mortality rate than the American studies. Bird et al. (12), who also controlled for confounders, failed to find a statistically significant difference in neonatal mortality rates between infants born late preterm and those born at 37 to 42 weeks; their sample was obtained from U.S. Medicaid

databases. Similarly, Melamed et al. (5) did not find statistically significant results in their tertiary care sample in Israel. In contrast, several smaller studies which did not control for confounders found significant risk for neonatal mortality (7, 8, 10, 11, 23).

2.2.2 Neonatal Outcomes of Early Term Birth

The most common reference group in studies of late preterm birth is infants born at term (i.e., 37 to 41 weeks). This comparison may be inappropriate if infants born early term are also at increased risk for poor outcomes compared to full term peers. The median gestational age at delivery is 39 weeks (with variation by labour onset and ethnicity) (27). Moreover, there is increasing evidence that the risk for poor neonatal outcomes does not level off until 39 to 41 weeks. (See Table 2.2 for a summary of these studies.)

General Indicators of Newborn Health

Most studies have shown increased risk for NICU admission among infants born early term. This evidence comes from three high quality retrospective cohort studies. In their Manitoba study, Ruth et al (3) found increased risk for NICU admission among infants born early term relative to those born at 39 to 40 weeks. In a study of data from the U.S. National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network, Tita et al. (28) also found increased risk for NICU admission at both 37 weeks and 38 weeks, relative to 39 weeks. (However, this study was limited to singleton elective caesarean sections.) In an Australian study of data from the National Perinatal Data Collection, Tracy et al. (29) showed increased risk for NICU admission at 37 and 38 weeks (vs. 40 weeks) for unassisted vaginal deliveries, for caesarean sections before labour, and for caesarean sections after labour in multiparas. For instrumental deliveries, results were not statistically significant at 38 weeks in primiparas and multiparas; the same was true for caesarean sections after labour in primiparas.

Only two studies examined length of stay during the birth hospitalization among infants born early term; both studies controlled for confounders but results were somewhat mixed. In their study of elective caesarean sections, Tita et al. (28) found increased risk for hospital stay more than 5 days at both 37 and 38 weeks. Dietz et al. (30) also found

increased risk for hospital stay of 4 or more days among infants born by caesarean section. Among infants born vaginally, results were statistically significant only for infants who were born at 37 weeks. (This study was conducted in a Medicaid population and was limited to low risk singleton deliveries.)

For Apgar scores, three high quality retrospective cohort studies showed mixed results. In their study of low risk singleton deliveries, Cheng et al. (31) used U.S. Vital Statistics data to show that infants born early term were at increased risk for 5-minute Apgar scores less than 7; results were not statistically significant for scores less than 4. Also using U.S. Vital Statistics data, Zhang and Kramer (32) measured 5-minute Apgar scores and found increased risk at 37 but not 38 weeks (vs. 40 weeks) for scores less than 7. Heimstad et al. (33) examined hospital databases in Norway and found increased risk for 1-minute and 5-minute Apgar scores less than 7 for infants born at 37 weeks but not 38 weeks.

Infants born early term are at increased risk for composite measures of morbidity; evidence for this comes from three high quality retrospective cohort studies. For example, Gouyon et al. (15) found that infants born early term were at increased risk for severe morbidity (i.e., death and/or severe neurological condition) at 37 but not 38 weeks. Ruth et al. (3) found that they were at increased risk for "any diagnosis" within a group of complications of prematurity. Finally, Tita et al. (28) found that infants born early term were at increased risk for any adverse outcome or death.

Respiratory Morbidity and Other Specific Diagnoses

Similar to infants born late preterm, most studies have found that infants born early term are at increased risk for neonatal respiratory morbidity. Evidence for this comes from several high quality retrospective cohort studies. The majority of these studies have shown increased risk for severe respiratory morbidity (15), respiratory distress syndrome (28), transient tachypnea of the newborn (28), hyaline membrane disease (31), pneumothorax (33), and ventilation use (31, 32) at both 37 and 38 weeks. In contrast, the Consortium on Safe Labour study found that infants born at 37 but not 38 weeks were at risk for respiratory distress syndrome, hyaline membrane disease, transient tachypnea of the newborn, pneumonia, and respiratory failure as well as use of surfactant, ventilators,

and oscillators (20). Ruth et al. (3) also found increased risk for respiratory distress syndrome at 37 but not 38 weeks. In a study of births at a single tertiary care centre in the U.S., Yoder et al. (21) did not find increased risk for a composite measure of respiratory morbidity at either 37 weeks or 38 weeks (relative to 39-40 weeks).

Fewer studies in the early term literature have examined other specific neonatal diagnoses. However, there is some evidence from high quality retrospective cohort studies that infants born early term are at increased risk for hyperbilirubinemia (3) sepsis (28), and hypoglycemia (28, 33). Zhang and Kramer (32) examined the occurrence of neurological morbidity (i.e., intraventricular hemorrhage or seizures) and did not find increased risk in infants born early term compared to those born at 40 weeks.

Neonatal Mortality

There is also some evidence that infants born early term are at increased risk for neonatal mortality compared to their full term peers, but only one study controlled for confounders. Zhang and Kramer (32) found that infants born at 37 and 38 weeks were at increased risk for neonatal mortality compared to those born at 40 weeks, but differences were small and were likely driven by extremely large sample sizes (7 million births). Three additional studies did not control for confounders. In their analysis of U.S. Vital Statistics records, Reddy et al. (24, 34) published two studies showing increased risk for neonatal mortality among infants born early term. In contrast, Young et al. (25), in their Utah study, found increased risk for neonatal mortality at 37 weeks but not 38 weeks.

2.2.3 Early Birth vs. Reasons for Early Birth

Early Birth

The argument for a relationship between physiological immaturity and risk of poor neonatal outcomes among infants born late preterm and early term is made on the basis of the observed dose-response relationship between gestational age and neonatal risk. Gouyon et al. (15), for example, found that the rate of severe respiratory morbidity declined steadily with increasing gestational age from 19.8% at 34 weeks to 0.28% at 39 to 41 weeks.

There is also evidence of functional immaturity of specific body systems at 34 to 36 weeks gestation, and neonatal morbidity associated with late preterm birth can be explained as follows:

- *Respiratory morbidity*. Infants born late preterm have immature lung volume and structure. This results in delayed fluid absorption, insufficient surfactant, and inefficient gas exchange (35-37).

- *Hyperbilirubinemia*. Infants born late preterm have increased bilirubin production and decreased bilirubin elimination. This is exacerbated by their poor suck-swallow mechanism, which results in inadequate breast milk intake, dehydration, and increased bilirubin circulation (35, 36).

- *Sepsis*. The immune systems of infants born late preterm are immature, and this is exacerbated by feeding difficulties which may prevent them from being breastfed (35).

- *Hypoglycemia*. Infants born late preterm have an immature system of glucose regulation; they may therefore not adapt adequately to the drop in glucose supply experienced immediately after birth with the removal of the placenta (35, 36).

- *Temperature instability*. Infants born late preterm have an immature epidermal barrier due to incomplete development of adipose tissue as well as a higher ratio of surface area to birth weight. They also have greater difficulty than term infants regulating their body temperature (35).

- *Neurological morbidity*. The brains and central nervous systems of infants born late preterm are under-developed and are more vulnerable to extrauterine insults, such as handling and ventilation, which may disrupt blood pressure and lead to bleeding in the brain (35, 38, 39).

There is little literature describing the functional immaturity of the body systems of infants born early term. However, fetal maturation is a continuous process with no threshold (40). Therefore, infants born early term would be expected to be

physiologically mature compared to their late preterm counterparts and immature compared to those born full term.

Reasons for Early Birth

Although the physiological immaturity of infants born late preterm and early term seems clear, it is possible that poor outcomes among these infants are associated not only with being born early but also with the reasons for being born early. Exposure to pathological conditions in utero may act through early birth to cause poor outcomes (41) and may even exacerbate the risk of poor outcomes among those born early (42, 43).

Studies conducted by Basso and Wilcox demonstrate the impact of the complex relationship between preterm birth and the reasons for preterm birth on neonatal outcomes. In the first study, Basso and Wilcox (42) estimated the overall expected proportion of neonatal mortality due to immaturity alone by summing gestational age-specific mortality rates among singletons with "optimal birth weight" for gestational age. They reasoned that mortality among these supposedly healthy infants must be due to immaturity and not the reasons for preterm birth (which would likely result in smaller birth weight for gestational age). They then compared this expected neonatal mortality rate with the actual neonatal mortality rate among U.S. singleton births (1995-2002). They concluded that 49% of neonatal mortality was due to immaturity alone and 51% of neonatal mortality was, in fact, due to underlying pathologies experienced in utero.

In a second study, Basso and Wilcox (43) simulated the effects of "unmeasured pathologies" on neonatal mortality. Each of these pathologies varied in their prevalence, impact on gestational age at birth, and impact on the likelihood of neonatal mortality. The results showed that these unmeasured pathologies increase the risk of mortality at any given preterm week. Moreover, factors with a strong direct effect on mortality can account for much of neonatal mortality among preterm infants even if the factor is rare.

Both of these studies provide a theoretical basis for examining not only the early birth itself but also factors leading to early birth when attempting to understand neonatal outcomes of late preterm and early term birth.

Medically Indicated vs. Spontaneous Preterm Birth

Some studies have attempted to address this issue by examining differences in outcomes among infants born late preterm following medically indicated vs. spontaneous birth. Medically indicated births are births in which the physician intervenes, through induction of labour or caesarean section before labour, when there is cause for concern due to maternal or fetal compromise. Among infants born preterm, medically indicated births are associated with a higher incidence of neonatal morbidity and mortality compared to spontaneous births. For example, in a study of U.S. Vital Statistics records, Chen et al. (44) found that, among births at 32 to 36 weeks, medically indicated births were at increased risk for early, late, and overall neonatal mortality as well as respiratory distress syndrome compared to spontaneous births. Similar results have been shown at earlier gestational ages; Lee et al. (45) found that, among infants born at 24 to 32 weeks, medically indicated births were at increased risk for respiratory distress syndrome and low Apgar scores compared to spontaneous births.

The distinction between medically indicated and spontaneous birth is useful for clinical practice since natural onset of labour is associated with hormonal changes which facilitate fetal lung maturation, thereby decreasing the risk of respiratory morbidity (24). However, categorizing births as spontaneous or medically indicated has limited etiological significance because maternal medical conditions are observed not only in medically indicated preterm births but also in spontaneous preterm births (46-50). This etiological overlap has been demonstrated in several studies. Ananth et al. (51), for example, showed that women with a first spontaneous preterm birth were not only more likely to experience a second spontaneous preterm birth but were also more likely to have a medically indicated preterm birth in a subsequent pregnancy. Moutquin et al. (46) estimated that medical and obstetrical complications were observed not only in medically indicated preterm birth (100%) but also in spontaneous preterm birth (28%). Indeed, specific conditions have been shown to be associated with both medically indicated and spontaneous birth. For instance, while Henderson et al. (49) found a strong association between medically indicated preterm birth and preeclampsia, small proportions of women with spontaneous preterm birth also had preeclampsia at all gestational ages. Likewise,

Berkowitz (52) found that antepartum hemorrhage is a significant risk factor for both spontaneous preterm birth and medically indicated preterm birth.

Further evidence supporting the assertion that a medically indicated vs. spontaneous birth dichotomy is an oversimplification comes from studies which have shown that, even among spontaneous births, those affected by maternal or obstetric complications are at increased risk for poor neonatal outcomes compared to spontaneous births without complications. Barros et al. (53), for example, found that relative to spontaneous births without maternal complications, those with maternal complications were at increased risk for neonatal mortality. Similarly, Villar et al. (54) found that both medically indicated births and spontaneous births with obstetric and medical complications had increased risk for intrapartum fetal death and neonatal mortality compared to spontaneous births with no obstetric or medical complications.

Because of the substantial etiological overlap between medically indicated and spontaneous births, the onset of labour (i.e., physician-initiated or spontaneous) should be seen as distinct from the presence of maternal medical conditions which contribute to a pathological intrauterine environment regardless of the nature of labour onset.

2.2.4 Proposed Neonatal Conceptual Model

The proposed conceptualization of the "biological determinants of preterm birth" that contribute to a pathological intrauterine environment regardless of the nature of labour onset is based on previous models described in the literature (55-60).

The "Preterm Parturition Syndrome" Models

In one of the most widely cited conceptualizations, Romero et al. (59, 61) described the "preterm parturition syndrome" as including infection, ischemia, endocrine disorders, uterine overdistension, cervical disease, abnormal allograft reaction, and allergic phenomena. However, this model includes some determinants which are relevant to only very preterm birth (e.g., cervical disease, allergic phenomena) and, with its focus on preterm labour, omits factors which may result in medically indicated birth (e.g., diabetes mellitus). Similar conceptualizations were described by others (55-58). Simmons et al.

(57) categorized pathways to preterm birth as infection and inflammation (intrauterine, lower genital tract, or systemic), decidual hemorrhage (thrombophilias, placental abruption, autoantibody syndromes), maternal/fetal hypothalamic-pituitary-adrenal activation (stress), pathological uterine overdistension (multifetal gestation, polyhydramnios), and cervical disease (cervical insufficiency). Lockwood et al. (55) and Menon et al. (56) described preterm births as being a result of four pathologic processes: activation of the maternal or fetal hypothalamic-pituitary-adrenal axis, decidual chorioamnionitis or systemic inflammation, decidual hemorrhage, and pathological distension of the uterus. All of these conceptualizations focused on the triggers of spontaneous preterm labour.

The "Phenotypic Classification" Model

Most recently, the Global Alliance to Prevent Prematurity and Stillbirth published a series of papers (60, 62, 63) promoting the adoption of a phenotypic classification system of preterm birth including maternal conditions (extrauterine infection, clinical chorioamnionitis, maternal trauma, worsening maternal disease, uterine rupture, and preeclampsia or eclampsia), fetal conditions (intrauterine fetal demise, fetal growth restriction, abnormal fetal heart rate, infection or fetal inflammatory response syndrome, fetal anomaly, alloimmune fetal anemia, polyhydramnios, and multiple fetuses), and placental pathological conditions (histological chorioamnionitis, placental abruption, placenta previa, and other placental abnormalities). This system is more all-encompassing and focuses on determinants of preterm birth that can lead to medically indicated birth or spontaneous birth. However, conditions are not grouped according to their possible biological mechanisms but rather by the broader origin of disease.

Hybrid Neonatal Model

The proposed conceptualization of the biological determinants of preterm birth used the following criteria to create a hybrid of existing models: (a) biological determinants of both spontaneous and medically indicated birth should be included; (b) only biological determinants relevant to late preterm and early term birth should be included; and (c) conditions should be categorized so that they represent an entity expected to operate

through the same pathophysiological mechanism (47, 63, 64). The proposed biological determinants of preterm birth include infection and inflammation (i.e., chorioamnionitis, bacterial vaginosis, other intrauterine or systemic infection, and premature rupture of the membranes), placental ischemia and other hypoxia (i.e., preeclampsia, eclampsia, chronic and gestational hypertension, fetal growth restriction, placenta previa, placental abruption, other bleeding, and vascular disease), endocrine triggers (i.e., depression, anxiety, and stress), and other biological determinants (i.e., pre-existing and gestational diabetes mellitus, polyhydramnios, and oligohydramnios). Each of these biological determinants of preterm birth is associated with early delivery and with poor neonatal outcomes and may therefore act through and with late preterm and early term birth to increase risk for neonatal morbidity and/or mortality.

Infection and inflammation, although more commonly associated with very preterm birth, have been implicated in late preterm birth (65). The detection of foreign microorganisms triggers the release of pro-inflammatory cytokines (e.g., IL-1 and tumour necrosis factor). These cytokines stimulate the production of prostaglandins, which, in turn, stimulate uterine contractility or degradation of the extracellular matrix of the fetal membranes, thus triggering labour (59, 66, 67). Pro-inflammatory cytokines can cross the blood-brain barrier and cause injury to the fetal brain resulting in a “fetal inflammatory response” (67-71) that is reflected in increased risk for respiratory morbidity (72-75), sepsis (74, 76), and hyperbilirubinemia (77).

Placental ischemia and other hypoxia are more commonly associated with late preterm birth (57). The precise trigger of spontaneous labour is unknown; however, when ischemia leads to decidual necrosis and hemorrhage, thrombin (a coagulation factor) may trigger labour (55, 58, 59, 78). Placental ischemia and other hypoxia are also associated with medically indicated birth (79). Reduced placental bloodflow caused by placental vascular lesions (as in preeclampsia and placental abruption) or placental insufficiency due to implantation of the placenta in a suboptimal location (as in placenta previa) may result in impaired oxygen and glucose delivery to the fetus, thus causing neonatal morbidity (69). Studies have found an association with composite measures of morbidity (73, 80), low Apgar scores (78, 80), NICU admission (81-84), respiratory morbidity (72,

73, 75, 81, 83, 85), hyperbilirubinemia (81), necrotizing enterocolitis (78, 86), and intraventricular hemorrhage (86).

Endocrine triggers have been associated with late preterm birth (57). Although the precise mechanism by which depression, anxiety, and stress induce spontaneous labour is still unknown, there is a role for corticotrophin-releasing hormone and activation of the maternal or fetal hypothalamic-pituitary-adrenal axis (55, 58, 59, 87). High levels of anxiety have also been implicated in medically indicated birth (88). Maternal distress may result in reduced bloodflow to the fetus due to the impact of cortisol on the placenta; morbidity may also occur because of hyperactivation of the fetal hypothalamic-pituitary-adrenal axis (89). Maternal depression and anxiety are associated with NICU admission (90) and neurological morbidity (91) in the infant.

There are other biological determinants that are more difficult to categorize because their mechanisms are more poorly understood. Diabetes mellitus is associated with birth before 37 weeks (92, 93), although there is controversy surrounding whether this is through caesarean delivery only or spontaneous labour as well (94). (Medically indicated birth associated with diabetes mellitus may be due to vascular or renal complications as well as macrosomia due to poor disease control (94).) Diabetes mellitus may result in neonatal morbidity via maternal and fetal hyperglycemia and hypoxia (93). An association has been found with NICU admission (94), low Apgar scores (95), respiratory distress, and neonatal mortality (95). Polyhydramnios and oligohydramnios may lead to spontaneous labour through a signal initiated by the mechanical stretch of the uterine myometrial, cervical, and fetal membranes through the cellular cytoskeleton. This activates cellular protein kinases such that the increase in intrauterine volume exceeds the ability of the uterus to handle the change (55, 59). Polyhydramnios and oligohydramnios have been found to be associated with NICU admission (82) and low Apgar scores (73).

These biological determinants of preterm birth contribute to a pathological intrauterine environment which may lead to early birth either via medically indicated delivery or spontaneous labour. As pathological processes, they also carry risks for neonatal morbidity and mortality. A greater understanding of the complex relationships among the

biological determinants of preterm birth, late preterm and early term birth, and neonatal morbidity and mortality may help to disentangle the causes of poor outcomes among infants born late preterm and early term. The relationships that this thesis proposes are shown in Figure 2.2, which depicts two complementary relationships between the biological determinants of preterm birth and gestational age, with implications for neonatal morbidity and mortality. This thesis proposes that:

1. The effect of gestational age on poor neonatal outcomes among late preterm and early term births is partially explained by biological determinants of preterm birth acting <u>through</u> early birth to produce poor outcomes; and

2. These biological determinants of preterm birth also <u>exacerbate</u> the effect of gestational age on poor neonatal outcomes.

Consideration of Biological Determinants of Preterm Birth by Previous Studies

The majority of the late preterm and early term literature has ignored the role of biological determinants of preterm birth or incompletely controlled for these factors in analyses. (See Table 2.3 for a summary of how the biological determinants of preterm birth were handled in the studies included in the literature review.) In the late preterm literature, 11 of the 23 studies ignored biological determinants of preterm birth altogether (7-11, 13, 21, 23-26). In the early term literature, the same was true for 3 of the 13 studies (25, 33, 34). However, even among the studies that did control for or exclude biological determinants of preterm birth to isolate the effect of gestational age (i.e., physiological immaturity), most only considered selected factors (e.g., hypertension or diabetes). Because of the heterogeneity of methods with which these biological determinants of preterm birth were handled, it is difficult to disentangle the effects of late preterm and early term birth per se on neonatal outcomes. It is more useful to purposefully examine the inter-relationship between gestational age and biological determinants of preterm birth on neonatal outcomes, since these factors are so intrinsically linked.

An exception is the study by Shapiro-Mendoza et al. (16) which examined records from the Massachusetts Pregnancy to Early Life Longitudinal data system. The authors

examined the risk of a high threshold composite of newborn morbidity according to gestational age (i.e., late preterm vs. term) and maternal morbidity (i.e., hypertensive disease, diabetes, antepartum hemorrhage, acute or chronic lung disease, maternal infection, cardiac disease, renal disease, or genital herpes vs. no exposure) as well as additive interactions between the two factors. They found that there was relative excess risk due to interaction for each maternal morbidity, except for maternal infection. A notable finding was that late preterm infants who were also exposed to maternal antepartum hemorrhage were 12 times more likely to have neonatal morbidity than term infants with no such exposure. (This was in comparison to the expected additive effect of 7.1.) This study adds strength to the argument that both early birth and the reasons for early birth may be important in predicting neonatal outcomes of late preterm and early term birth and that maternal morbidity could exacerbate the effect of late preterm (or early term) birth on neonatal outcomes. Unfortunately, this study is the only one to date which has addressed this issue among late preterm births.

By ignoring these biological determinants of preterm birth, previous studies may have missed the true etiology of morbidity among infants born late preterm and early term. The proposed conceptual model allows for an examination of gestational age as an intermediate factor and as a factor which may interact with the reasons for preterm birth to produce poor outcomes.

2.3 Developmental Outcomes

2.3.1 Developmental Outcomes of Late Preterm Birth

Fewer studies have examined developmental outcomes of children born late preterm. Studies have examined several developmental outcomes, including developmental delays, poor academic performance and low IQ, and specific diagnoses, with variable results. A summary of these studies is included in Table 2.4.

Developmental Delays

Children born late preterm may be at increased risk for general developmental delay compared to children born at term. Evidence for this comes from several prospective or

retrospective cohort studies, characterized by large sample sizes; population-based data from administrative datasets, large-scale surveys, or several secondary and tertiary care clinical centres; and analytic control of potential confounders (hereinafter referred to as "high quality" studies). In a U.S. study of data from the Children's Medical Services' Early Intervention Program, for example, Morse et al. (96) found that, compared to children born at 39 to 41 weeks, children born late preterm were at increased risk for developmental delay or disability at 3 and 4 years of age. This study was restricted to children who were healthy at birth by excluding children with a birth hospitalization of more than 3 days or transfer to another hospital. Woythaler et al. (97) found increased risk at 24 months (vs. children born at 37 weeks or later) in a secondary analysis of the U.S. Early Childhood Longitudinal Study (Birth Cohort). Shapiro-Mendoza et al. (98) found similar results at 5 years; however, they measured developmental delay by early intervention program enrollment and may have missed cases of mild developmental delay not receiving services. Evidence also comes from studies with limitations to their study designs. Petrini et al. (99), for example, found that children born late preterm were at increased risk for developmental delay at 5 years compared to children born at 37 to 41 weeks; however, they used a low socioeconomic sample from the U.S. Kaiser Permanente Medical Care Program.

Results have been more variable when assessing motor and social delays separately. Although Woythaler et al. (97) found increased risk for motor delay at 24 months, three other studies failed to find statistically significant risks for this outcome. Two of these studies were high quality secondary analyses of large, national surveys. The null findings of a study using data from the U.S. Early Childhood Longitudinal Study (Birth Cohort) by Nepomnyaschy et al. (100) are possibly explained by exclusion of births with a hospital stay more than 3 days or transfer to another hospital at birth; however, an analysis of the U.K. Millennium Cohort Study by Quigley et al. (101), which made no such exclusions, also failed to find statistically significant results. An analysis of births in a single U.S. tertiary care centre by Baron et al. (102), which had a small sample size, did not find statistically significant results. Three studies examining social delays all failed to find statistically significant risks associated with late preterm birth. These null findings came from the Early Childhood Longitudinal Study (100) and the Millennium Cohort

Study (101). The third study, an analysis of data from the U.S. National Institutes of Child Health and Human Development Study of Early Child Care and Youth Development by Gurka et al. (103) also did not find statistically significant results at 4 to 15 years of age; however, this study was smaller and may have been under-powered.

Poor Academic Performance and Low IQ

Studies generally show that children born late preterm are at increased risk for poor academic performance as measured by tests of language, reading, and mathematical aptitude. Evidence for this comes from several high quality studies. In a secondary analysis of the U.S. Early Childhood Longitudinal Study (Kindergarten Cohort), Chyi et al. (104) found that, compared to children born at 37 weeks or later, children born late preterm were at increased risk for poor reading and math scores. (Children with "neonatal compromise" [i.e., anoxia or respiratory distress] were excluded from this analysis.) Lipkind et al. (105) found similar increased risks for poor reading and math scores at 8 years of age; they used data from the U.S. Longitudinal Study of Early Development. Several other studies have found increased risk for poor language, reading, and math scores at 4 (100) and 5 (101) years of age and poor reading and math scores at 6 years of age (106). In an analysis of the U.K. Millennium Cohort Study, Poulsen et al. (107) found increased risk for poor reading scores but not poor math scores at 7 years of age (relative to children born at 39 to 41 weeks). In another U.K. study, Silva et al. (108) used data from the British Birth Cohort Study and did not find increased risk for poor language, reading, or math scores; however, their outcome was assessed at 10 years of age and their study was limited by a 35% drop-out rate which biased the final study sample toward a high socioeconomic group.

Several high quality studies have also assessed other measures of academic performance, including use of special education; results mostly show increased risk for poor outcomes for children born late preterm. For example, Chyi et al. (104) found that children born late preterm were at increased risk for needing individualized education plans in grade 1 and special education in Kindergarten and grade 1. Similarly, Lipkind et al. (105) found increased risk for special education at 8 years of age among children born late preterm,

and Poulsen et al. (107) found increased risk for poor school readiness at 3 years of age. In their analysis of data from the Children's Medical Services' Early Intervention Program, Morse et al. (95) found increased risk for grade retention in Kindergarten and suspension in Kindergarten but no differences in "ready to start school" status.

Results for tests of intelligence have been more mixed. However, these studies have been smaller and/or limited to tertiary care samples. In their analysis of the U.S. National Institutes of Child Health and Human Development Study of Early Child Care and Youth Development, Gurka et al. (103) did not find increased risk for low verbal IQ among 4 to 15 year old children born late preterm. Baron et al. (102) did not find increased risk for low verbal and non-verbal IQ at 3 years; their sample was limited to a small sample of births from a single U.S. tertiary care centre. Finally, Talge et al. (109) found statistically significant results for overall IQ and non-verbal IQ but not verbal IQ; their sample was limited to high risk births from two U.S. hospitals. All three studies were characterized by small sample sizes.

Specific Diagnoses

Several studies have examined specific diagnoses indicative of poor development as possible outcomes of late preterm birth. Petrini et al. (99) found that 5-year-old children who were born late preterm were at increased risk for cerebral palsy, intellectual disability, and seizure disorders. Linnet et al. (110) conducted a nested case-control study of birth and psychiatric registry data in Denmark. They found that children born late preterm were at increased risk for attention deficit / hyperactivity disorder. However, the association disappeared once the authors excluded children whose parents had a history of mental disorders as well as children with conduct disorders. Using U.S. birth and education data, Harris et al. (111) also failed to find increased risk for attention deficit / hyperactivity disorder and learning disability at 5 years of age.

2.3.2 Developmental Outcomes of Early Term Birth

There are only a handful of studies comparing children born early term to those born "full" term. These studies show conflicting findings regarding risks for poor

developmental outcomes, making it difficult to draw conclusions. A summary of these studies can be found in Table 2.5.

Developmental Delays

To our knowledge, only two studies meeting the inclusion criteria for this review examined the risk for developmental delays among children born early term. In their study of the U.S. Pregnancy to Early Life Longitudinal Data System, Shapiro-Mendoza et al. (98) showed that children born early term were more likely than those born at 39 to 41 weeks to have a developmental delay at 5 years of age. Quigley et al. (101) examined motor and social development separately and found that children born early term were at increased risk for social but not motor developmental delay at 5 years of age.

Poor Academic Performance and Low IQ

More studies have examined performance on tests of reading and math, with variable results. Most of this evidence comes from high quality secondary analyses of national surveys. Two studies came from the U.K. Millennium Cohort Study. In the first study, Quigley et al. (101) found that children born early term were at increased risk for poor language scores but not poor math scores at 5 years of age. Poulsen et al. (107) failed to find increased risk for poor reading or math scores at 7 years of age. Additional studies also had conflicting findings. Noble et al. (112) examined data from the New York Department of Health and Hygiene and the Board of Education and found that children born early term were at increased risk for poor reading and math scores at 8 years of age. In contrast, in a secondary analysis of the Promotion of Breastfeeding Intervention Trial in Belarus, Yang et al. (113) found that risks of poor reading and math scores at 6 years of age were small and not statistically significant. (This sample had a lower socioeconomic status than samples used by the U.S. and U.K. studies.)

Again, there is little research examining more general measures of school performance such as special education use and intelligence. In one study, Poulsen et al. (107) failed to find increased risk associated with early term birth for poor school readiness at 3 years of age. In their secondary analysis of the Belarus randomized controlled trial, Yang et al.

(113) found increased risk for low overall IQ at 37 but not 38 weeks. This difference was driven by non-verbal IQ; there were no differences in verbal IQ at 37 or 38 weeks.

2.3.3 Early Birth vs. Factors Associated with Early Birth

Early Birth

Similar to neonatal outcomes, many studies argue that physiological immaturity explains the risks of poor developmental outcomes associated with late preterm and early term birth. This is based on evidence of a dose-response relationship between gestational age and risk of developmental problems; Morse et al. (96), for instance, found a decline in the percentage of children with developmental delay as gestational age increased.

Moreover, 34 to 40 weeks gestation is a critical period of rapid fetal brain development: cortical volume increases by 50%, the proportion of gray matter and myelinated white matter to total brain volume increases, and the cerebellum grows by 25% (114, 115). Imaging studies have shown that infants born late preterm have smaller gray matter volume than infants born at term despite having a normal head circumference (116). Moreover, longer gestation is associated with increases in gray matter in the temporal and parietal lobes evident even in 6 to 10 year olds born at term (117).

Early birth poses a threat to optimal brain development, because of the early disruption of intrauterine stimuli and nutrition (118-120) and because of the vulnerability of the premature brain to pathologic extrauterine events (e.g., neonatal morbidity) (120). It is therefore plausible that even mildly premature birth would have a lasting impact on development. Thus the question posed in studies of late preterm and early term birth is a fundamentally biological one: Do the incomplete in utero development and early exposure to the extrauterine environment associated with mild prematurity result in neurological damage that causes suboptimal development in early childhood?

Factors Associated with Early Birth

Although the pathway of interest is biological, its realization is more complex because children do not develop in isolation, and the role of the social environment becomes

increasingly important as the child ages (121, 122). There is a large body of literature supporting the importance of social factors in determining developmental outcomes. Moreover, research has shown that the social environment is multi-dimensional; its complexity cannot be captured by accounting only for a mother's education and income level (122). In addition to socio-demographic and socioeconomic characteristics, parenting, maternal health and mental health, and the home environment are all strong predictors of developmental outcomes (123).

One of the most important social factors is parenting. Parenting can be described in terms of positive and negative parenting practices. Positive parenting is characterized by warmth, responsiveness, and social and intellectual stimulation, while negative parenting is characterized by hostility, disapproval, and inconsistency (124). Parenting has been shown to be associated with developmental outcomes, with positive parenting being protective against and negative parenting being predictive of developmental delays (125) and suboptimal academic performance (126). Parenting is thought to be the mechanism through which the social context exerts its influence on child development. For example, Belsky et al. (127) showed that some of the variance in parenting variables was explained by maternal income, education, age, and partnership status. Parents with low socioeconomic status may have poor parenting skills because of stress associated with low income or because of a lack of resources to engage in nurturing behaviours (128, 129). Maternal mental health, which has also been shown to be associated with motor and social development (130, 131) and school readiness (132) is also thought to act through parenting practices (121, 132) since mothers who are depressed may show higher levels of hostility and lower levels of emotional availability than non-depressed mothers (132). Thus, as an important proximal determinant of development, parenting must be taken into consideration in studies of child outcomes of late preterm and early term birth.

This is especially important because social disadvantage is also associated with early birth. Numerous studies have shown a relationship between low education or low income and preterm birth, even in high income countries (66, 133). Studies of children born late preterm specifically have shown an association with social disadvantage. Morse et al. (96), for example, showed that mothers of children born late preterm were more likely to

be younger and to have a lower education during pregnancy. Similarly, van Baar et al. (134) examined children born at 32 to 36 weeks gestation, and found that their mothers were less likely than mothers of children born at 37 to 43 weeks gestation to have post-secondary education. These associations underscore the importance of properly taking into account the full effects of the social environment to delineate the specific effect of gestational age on developmental outcomes.

2.3.4 Proposed Developmental Conceptual Model

Because of the complexity of these factors, a theory is needed to "organize" the influences on child development. Ideally, such a theory would explain the separate and combined effects of biology (i.e., biological determinants of preterm birth, gestational age, neonatal morbidity) and social factors on developmental outcomes. In keeping with this, an initial scan of the literature was performed to identify theories related to child development (135-139). These theories were examined in detail to select theories which would best reflect the objective of isolating the effect of gestational age on developmental outcomes within the context of social risk factors. Ultimately, Bronfenbrenner's bioecological theory (137) and Escalona's concept of double jeopardy (138) were chosen to support this objective.

Bronfenbrenner's Bioecological Theory

The basic principles of bioecological theory find their roots in ecology, the study of the relationships between organisms and their external environments. In this case, the study is of the child and his or her "habitat" (i.e., the home, school, or neighbourhood, depending on the child's age) as well as the linkages among these spheres of influence. Bronfenbrenner's theory thus acknowledges the interplay between biology and society (137). Bronfenbrenner's theory is referred to as a "person-process-context-time" theory, in reference to its four main components:

- *Person* refers to the characteristics of the child which encourage or discourage interactions with the social environment. These include temperament, abilities, and attributes (e.g., sex, age, disability status) (137).

- *Process* describes the ongoing interactions between the child and the environment; these interactions are the primary mechanisms of development. The main proximal social process, during the early years, is parenting. The concept of process acknowledges the reciprocal relationship between the child and his or her immediate environment (e.g., interactions in a child-parent relationship). Proximal social processes such as parenting can produce competence (i.e., further development of language, skills, or abilities) or dysfunction (i.e., delays in different domains of development) (137).

- *Context* refers to the social environment in which proximal social processes operate. Bronfenbrenner differentiated among the layers of the social context and the relationships between them. The microsystem refers to the immediate settings in which the child develops. In the early years, the home is the main microsystem; its characteristics are family structure (i.e., parental partnership status, number of siblings), family resources (i.e., family income, parental occupation, parental education, parental age, parental health and mental health), social support, and family functioning (140, 141). As the child develops, he or she becomes exposed to additional microsystems (e.g., daycare, school). The mesosystem describes the relationships among these settings (e.g., parent-teacher interactions) (140). The exosystem refers to settings that indirectly affect child development (e.g., parents' workplaces, school boards, planning commissions). Finally, the macrosystem refers to the broader political, cultural, and economic context (137).

- Child development occurs across *time*. Bronfenbrenner distinguished between microtime (i.e., the time for a specific activity), mesotime (i.e., the consistency of these activities across a child's development), and macrotime (i.e., how developmental processes vary depending on the historic context) (137).

Escalona's Concept of Double Jeopardy

The concept of "double jeopardy" enhances bioecological theory by capturing the idea that children who have both biological and social risk factors are at even greater risk for poor outcomes compared to those with only biological or only social risk factors (138).

The idea was first introduced by Escalona, who studied developmental outcomes of very low birth weight infants. He found that infants in low socioeconomic households showed a dramatic cognitive decline in the second year of life. In contrast, infants in the highest socioeconomic group, although experiencing a slight decrease in mean IQ at 28 months, showed full recovery thereafter (138). Although this study had no term reference group, Escalona suggested that preterm infants respond more drastically than term infants to social risk factors (138). This assertion was confirmed by subsequent studies (142-144).

Hybrid Developmental Model

To address a fundamentally biological question that nevertheless occurs in a social context, the proposed conceptual model relies on a "hybrid" theory, combining components of (a) biological evidence of neurological development during the late preterm and early term periods; (b) Bronfenbrenner's bioecological theory; and (c) Escalona's concept of double jeopardy.

Biological evidence of rapid neurological development in the final weeks of gestation suggests vulnerability of infants born late preterm and early term to poor developmental outcomes due to early interruption of intrauterine nutrition and stimuli and exposure to pathological extrauterine events such as neonatal morbidity. Bronfenbrenner's bioecological theory establishes the social nature of child development and distinguishes between social context variables and proximal social processes. The proposed conceptual model focuses on the microsystem of the home, thus limiting attention to early development. Thus, the proximal social process of interest is parenting, since this is the most important process in early development. Finally, Escalona's concept of double jeopardy is used to emphasize how social factors may moderate the effect of mild prematurity on developmental outcomes. Although other social factors such as socioeconomic status have been shown to interact with gestational age (142-144), we focus on parenting as the moderator of interest because (a) parenting most directly affects child development (127) and (b) parenting, unlike socioeconomic status, is modifiable and can be a target health for public health initiatives. (Social context variables should nevertheless be controlled for, as shown in the conceptual model.)

By examining the independent and joint effects of gestational age and proximal social processes on developmental outcomes, it may be possible to better determine the extent to which poor developmental outcomes among children born late preterm or early term are due to physiological immaturity at birth alone or to a combination of physiological immaturity and social factors. The proposed relationships are shown in Figure 2.3. This thesis proposes that:

1. The effect of gestational age on poor developmental outcomes among late preterm and early term births can only be isolated after taking into account all aspects of the social environment, including social context variables and proximal social processes.

2. These proximal social processes, as measured by poor parenting, exacerbate the effect of gestational age on poor developmental outcomes.

Consideration of Social Factors by Previous Studies

Most previous studies investigating developmental outcomes of late preterm and early term birth have overlooked or downplayed, to varying degrees, the role of social factors in determining the risk of these outcomes. (Refer to Table 2.6 for a summary of how proximal social processes and social context variables were handled by these studies.) Many studies only controlled for markers of socioeconomic status (e.g., parental income or occupation, education) and maternal age or partnership status. This was true of 14 of the 16 studies included in the late preterm literature review (96, 98-102, 104-111) and all 5 studies included in the early term literature review (98, 101, 107, 112, 113). This reflects the biomedical model of disease, which tends to ignore social influences on development (141, 145).

Only a handful of studies controlled for more immediate components of the social context. Gurka et al. (103) controlled for maternal mental health and family functioning. (This study actually failed to find any association between late preterm birth and poor developmental outcomes.) Woythaler et al. (97) controlled for maternal mental health. None of the studies included in the literature review considered the role of parenting in

determining risk for poor developmental outcomes and may have therefore not been truly able to isolate the effect of gestational age on developmental outcomes.

Moreover, none of the studies examined interactions between gestational age and social risk factors. Such an analysis has been carried out in studies with wide definitions of late preterm birth. Nomura et al. (144) found that individuals born at 33 to 37 weeks gestation were more likely than those born at term to have poor learning-related abilities (e.g., IQ, reading, math, spelling) at 7 years of age and poor educational attainment (e.g., grade repetition, years of education, degrees) in adulthood only if they were born below the poverty line. Ekeus et al. (143) found a statistically significant interaction between gestational age (33 to 36 weeks) and socioeconomic status in predicting intellectual performance among 19 year old Swedish conscripts. Similarly, Lindstrom et al. (142) found that the effect of gestational age (33 to 36 weeks and 37 to 38 weeks) on educational attainment of 23 to 29 year olds in Sweden was greater in low socioeconomic compared to high socioeconomic households. As described previously, similar interactions would be expected with poor parenting, a stronger influence on early development.

By downplaying proximal social processes, and even social context variables, previous studies may have misestimated the effect of gestational age per se on poor developmental outcomes among children born late preterm and early term. The proposed conceptual model allows for an examination of gestational age within the context of a social environment described by social context variables and proximal social processes.

2.4 Conclusion

To our knowledge, this is the first study to develop conceptual models to examine, in depth, factors that may explain or exacerbate the relationship between mild prematurity and poor neonatal and developmental outcomes. By doing so, this thesis contributes to the literature by (a) providing a coherent framework with which to explain the relationships among variables thought to affect outcomes of late preterm and early term birth and (b) forming hypotheses around the existence of high risk groups in the late preterm and early term population.

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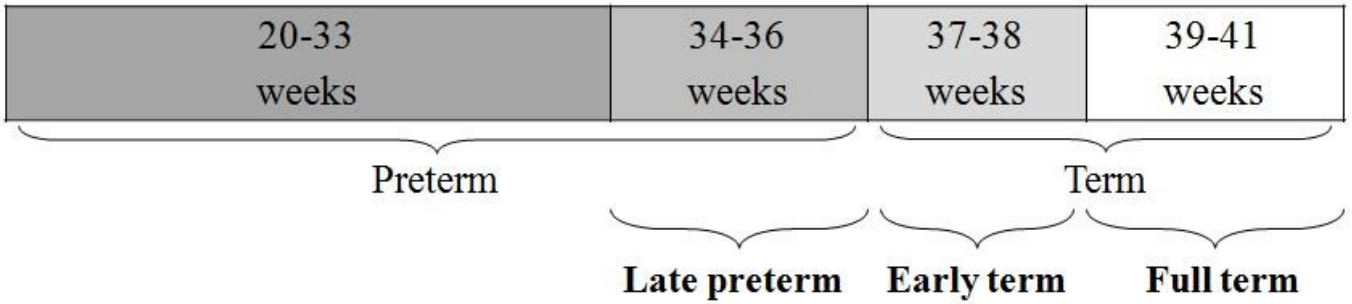
Figure 2.1. Labels Associated with Gestational Age Periods.



* Definitions in bold are consistent with U.S. National Institute of Child Health and Human Development definitions (2). Figure is not to scale.

Figure 2.2. Conceptual Model of Neonatal Outcomes of Infants Born Late Preterm and Early Term.

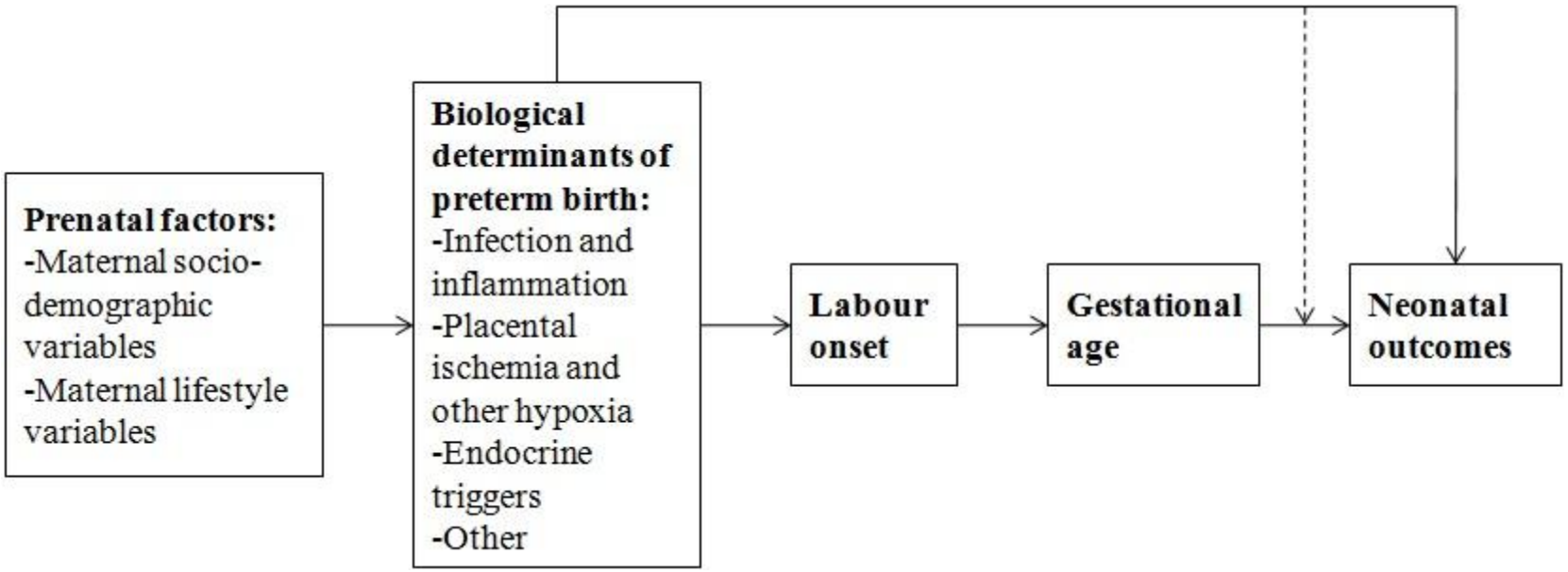


Figure 2.3. Conceptual Model of Developmental Outcomes of Children Born Late Preterm and Early Term.

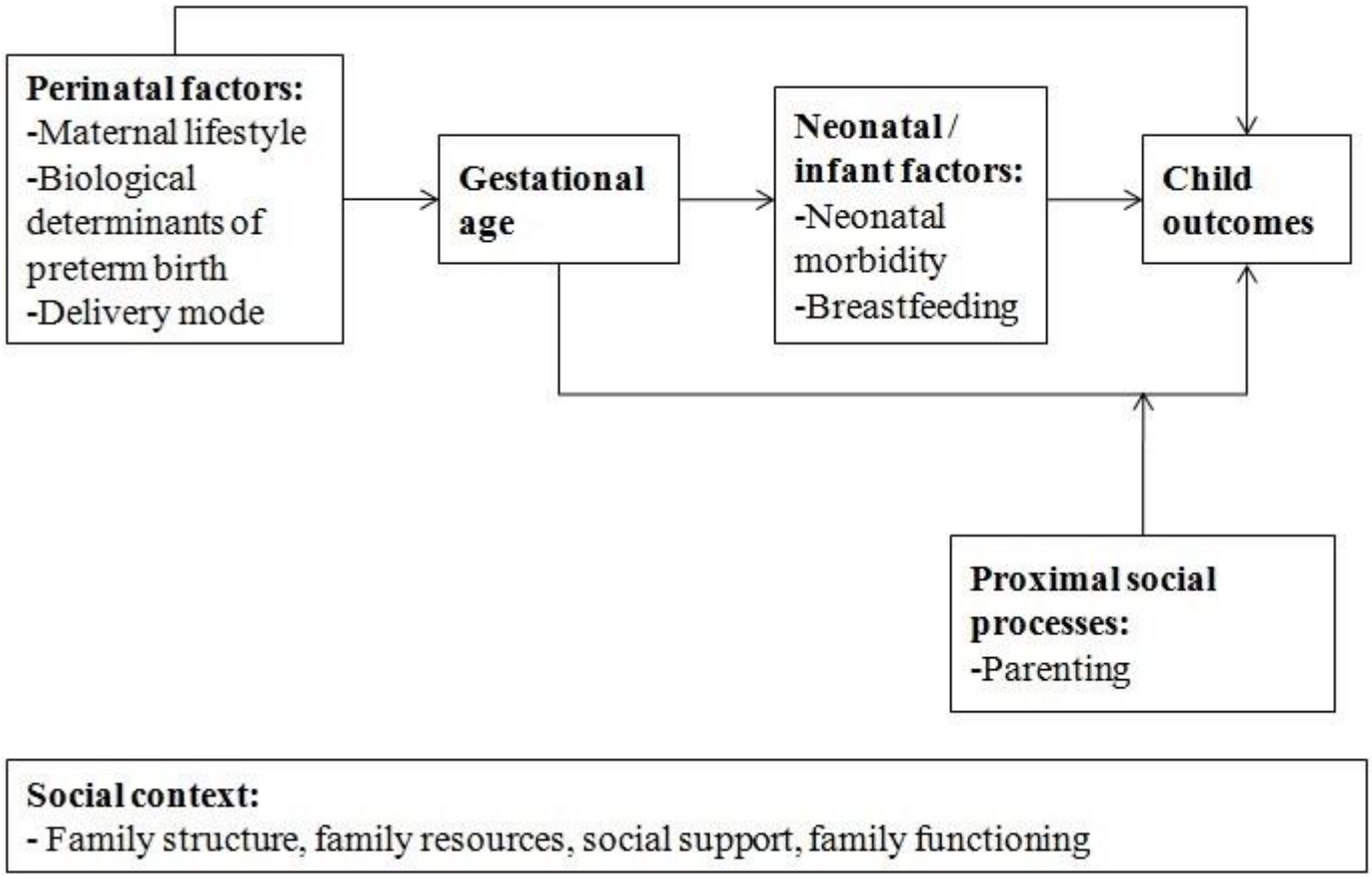


Table 2.1. Summary of Studies Examining Association between Late Preterm Birth and Poor Neonatal Outcomes.

Authors	Reference group	Design	N	Adjusted estimates	Outcomes significantly associated	Outcomes not significantly associated
Bastek (2008)	≥37 weeks	Retrospective cohort (U.S., 2002-2005)	203	Yes	Composite, respiratory morbidity, jaundice, hypoglycemia	Sepsis, temperature instability, NEC, neurological morbidity
Bird (2010)	37-42 weeks	Retrospective cohort (U.S., 2001-2005)	20,491	Yes	Longer stay, respiratory morbidity, jaundice, sepsis, hypoglycemia, temperature instability, neurological morbidity	Mortality
Celik (2012)	37-41 weeks	Prospective cohort (T.R., 2010-2011)	17,516	No	NICU admission, respiratory morbidity, jaundice, hypoglycemia, mortality	Sepsis
Cheng (2011)	37-40 weeks	Retrospective cohort (U.S., 2005)	3,167,615	Yes	NICU admission, low Apgar, respiratory morbidity, sepsis, neurological morbidity	
Consortium (2010)	39-40 weeks	Retrospective cohort (U.S., 2002-2008)	185,327	Yes	Respiratory morbidity	
De Almeida (2007)	37-41 weeks	Retrospective cohort (B.R., 2003)	10,774	Yes	Respiratory morbidity	
Femitha (2011)	≥37 weeks	Retrospective cohort (I.N., 2010)	500	No	Composite, respiratory morbidity, jaundice, sepsis, hypoglycemia, NEC, neurological morbidity	

Authors	Reference group	Design	N	Adjusted estimates	Outcomes significantly associated	Outcomes not significantly associated
Gouyon (2010)	39-41 weeks	Retrospective cohort (F.R., 2000-2008)	150,426	Yes	Composite, respiratory morbidity	
Jaiswal (2010)	37-41 weeks	Prospective cohort (I.N., 2009)	3,070	Yes	Composite, respiratory morbidity, jaundice, sepsis, hypoglycemia	
Kalyoncu (2010)	37-41 weeks	Retrospective cohort (T.R., 2005-2007)	504	No	Respiratory morbidity, sepsis, hypoglycemia, temperature instability, NEC, mortality	Neurological morbidity
Kitsommart (2009)	≥37 weeks	Retrospective cohort (C.A., 2004-2008)	9,859	No	NICU admission, respiratory morbidity, mortality	
Kramer (2000)	≥37 weeks	Retrospective cohort (C.A., 1985-1994)	1,419,014	Yes	Mortality	
Leone (2012)	39-40 weeks	Retrospective cohort (C.H., 2006-2007)	2,196	No	Longer stay, composite, respiratory morbidity, jaundice, hypoglycemia, temperature instability	Low Apgar
Lubow (2009)	37-41 weeks	Retrospective cohort (U.S., 2005-2006)	299	No	NICU admission, longer stay, respiratory morbidity, jaundice, sepsis	Hypoglycemia

Authors	Reference group	Design	N	Adjusted estimates	Outcomes significantly associated	Outcomes not significantly associated
McIntire (2008)	39 weeks	Retrospective cohort (U.S., 1998-2005)	133,022	No	NICU admission, longer stay, composite, respiratory morbidity, jaundice, NEC (34, 35), neurological morbidity, mortality	Low Apgar, NEC (36)
Melamed (2009)	37-40 weeks	Retrospective cohort (I.L., 1997-2006)	9,912	Yes	NICU admission, longer stay, composite, respiratory morbidity, jaundice, sepsis, hypoglycemia, temperature instability, NEC	Mortality
Reddy (2009)	39-40 weeks	Retrospective cohort (U.S., 2001)	292,627	No	Mortality	
Ruth (2012)	39-40 weeks	Retrospective cohort (C.A., 2004-2006)	25,312	Yes	NICU admission, composite, respiratory morbidity, jaundice	
Santos (2008)	37-41 weeks	Prospective cohort (B.R., 2004)	4,134	Yes	Composite, NICU admission, low Apgar, mortality	
Shapiro-Mendoza (2008)	37-41 weeks	Retrospective cohort (U.S., 1998-2003)	445,917	Yes	Composite	
Tsai (2012)	37-40 weeks	Retrospective cohort (T.W., 2008-2009)	7,421	No	NICU admission, longer stay, respiratory morbidity, jaundice, sepsis, hypoglycemia, temperature instability, mortality	

Authors	Reference group	Design	N	Adjusted estimates	Outcomes significantly associated	Outcomes not significantly associated
Yoder (2008)	39-40 weeks	Retrospective cohort (U.S., 1990-1998)	11,532	Yes	Respiratory morbidity	
Young (2007)	40 weeks	Retrospective cohort (U.S., 1999-2004)	282,894	No	Mortality	

NEC: Necrotizing enterocolitis

Table 2.2. Summary of Studies Examining Assocation between Early Term Birth and Poor Neonatal Outcomes.

Authors	Reference group	Design	N	Adjusted estimates	Outcomes significant associated	Outcomes not significantly associated
Cheng (2008)	39 weeks	Retrospective cohort (U.S., 2003)	1,463,623	Yes	Low Apgar, respiratory morbidity	
Consortium (2010)	39-40 weeks	Retrospective cohort (U.S., 2002-2008)	185,327	Yes	Respiratory morbidity (37)	Respiratory morbidity (38)
Dietz (2012)	39-40 weeks	Retrospective cohort (U.S., 1998-2007)	22,420	Yes	Longer stay (37)	Longer stay (38)
Gouyon (2010)	39-41 weeks	Retrospective cohort (F.R., 2000-2008)	150,426	Yes	Composite (37), respiratory morbidity	Composite (38)
Heimstad (2006)	39 weeks	Retrospective cohort (N.O., 1990-2001)	27,514	Yes	Low Apgar (37), respiratory morbidity, hypoglycemia	Low Apgar (38)
Reddy (2009)	39-40 weeks	Retrospective cohort (U.S., 2001)	292,627	No	Mortality	
Reddy (2011)	40 weeks	Retrospective cohort (U.S., 1995-2006)	46,329,018	No	Mortality	

Authors	Reference group	Design	N	Adjusted estimates	Outcomes significant associated	Outcomes not significantly associated
Ruth (2012)	39-40 weeks	Retrospective cohort (C.A., 2004-2006)	25,312	Yes	NICU admission, composite, respiratory morbidity, jaundice	
Tita (2010)	39 weeks	Retrospective cohort (U.S., 1999-2001)	11,255	Yes	NICU admission, longer stay, composite, respiratory morbidity, sepsis, hypoglycemia	
Tracy (2007)	40 weeks	Retrospective cohort (A.U., --)	481,362	Yes	NICU admission	
Yoder (2008)	39-40 weeks	Retrospective cohort (U.S., 1990-1998)	11,532	Yes		Respiratory morbidity
Young (2007)	40 weeks	Retrospective cohort (U.S., 1999-2004)	282,894	No	Mortality (37)	Mortality (38)
Zhang (2009)	40 weeks	Retrospective cohort (U.S., 1995-2001)	7,081,737	Yes	Low Apgar (37), respiratory morbidity, mortality	Low Apgar (38), neurological morbidity

Table 2.3. Previous Consideration of Biological Determinants of Preterm Birth.

Authors	Infection and inflammation	Placental ischemia and other hypoxia	Endocrine triggers	Other biological determinants
Bastek (2008)	Contr: Chorioamnionitis, PROM	Excl: Preeclampsia, abruption	---	---
Bird (2010)	Contr: Fever, PROM	Contr: Hypertension, eclampsia, abruption, bleeding	---	Contr: Diabetes, hydramnios
Celik (2012)	---	---	---	---
Cheng (2008)	---	Excl: Hypertension	---	Excl: Diabetes
Cheng (2011)	Excl: PROM	Excl: Hypertension, preeclampsia, abruption, previa	---	Excl: Diabetes
Consortium (2010)	---	Contr: Hypertension	---	Contr: Diabetes
De Almeida (2007)	Contr: Nonclear amniotic fluid	Contr: Hypertension	---	---
Dietz (2012)	---	Excl: Hypertension, SGA	---	Excl: Diabetes
Femitha (2011)	---	---	---	---
Gouyon (2010)	Contr: Chorioamnionitis, PROM	Contr: Hypertension, abruption, previa, IUGR	---	Contr: Diabetes
Heimstad (2006)	---	---	---	---

Authors	Infection and inflammation	Placental ischemia and other hypoxia	Endocrine triggers	Other biological determinants
Jaiswal (2010)	---	Contr: IUGR	---	---
Kalyoncu (2010)	---	---	---	---
Kitsommart (2009)	---	---	---	---
Kramer (2000)	---	---	---	---
Leone (2012)	---	---	---	---
Lubow (2009)	---	---	---	---
McIntire (2008)	---	---	---	---
Melamed (2009)	Excl: Chorioamnionitis, fever, PROM	Excl: Hypertension, preeclampsia, abruption, previa, IUGR	---	Excl: Diabetes, hydramnios
Morrisson (1995)	Contr: Chorioamnionitis	Contr: Preeclampsia, IUGR	---	Contr: Diabetes
Reddy (2009)	---	---	---	---
Reddy (2011)	---	---	---	---
Ruth (2012)	---	Contr: IUGR	---	---
Santos (2008)	Contr: Infection	Contr: Hypertension, bleeding	---	Contr: Diabetes
Shapiro-Mendoza (2008)	RERI: Maternal infection, genital herpes	RERI: Hypertension, antepartum hemorrhage	---	RERI: Diabetes

Authors	Infection and inflammation	Placental ischemia and other hypoxia	Endocrine triggers	Other biological determinants
Tita (2010)	Excl: Not specified	Excl: Not specified	Excl: Not specified	Excl: Not specified
Tomashek (2006)	Contr: Not specified	Contr: Not specified	Contr: Not specified	Contr: Not specified
Tracy (2007)	---	Excl: Hypertension, SGA	---	Excl: Diabetes
Tsai (2012)	---	---	---	---
Yoder (2008)	---	---	---	---
Young (2007)	---	---	---	---
Zhang (2009)	---	Contr: Hypertension, eclampsia	---	Contr: Diabetes

Contr: Controlled for; Excl: Excluded; RERI: Relative excess risk due to interaction; IUGR: Intrauterine growth restriction; PROM: Premature rupture of the membranes; SGA: Small for gestational age.

Table 2.4. Summary of Studies Examining Association between Late Preterm Birth and Poor Developmental Outcomes.

Authors	Reference group	Design	N	Adjusted estimates	Outcomes significant associated	Outcomes not significantly associated
Baron (2009)	≥37 weeks	Retrospective cohort (U.S., 2004-2005)	95	Yes		Verbal IQ, nonverbal IQ, motor developmental delay
Chyi (2008)	≥37 weeks	Prospective cohort (U.S., 1993-1994)	14,438	Yes	Poor reading scores, poor math scores, special education	
Gurka (2010)	37-41 weeks	Prospective cohort (U.S., 1991)	1,298	Yes		Verbal IQ, social developmental delay
Harris (2013)	37-41 weeks	Retrospective cohort (U.S., 1976-1982)	5,699	Yes		Attention deficit / hyperactivity disorder, learning disability
Linnet (2007)	40-42 weeks	Nested case-control (D.K., 1980-1994)	20,834	Yes	Attention deficit / hyperactivity disorder	
Lipkind (2012)	37-42 weeks	Prospective cohort (U.S., 1994-1998)	212,806	Yes	Poor reading scores, poor math scores, special education	
Morse (2009)	37-41 weeks	Retrospective cohort (U.S., 1996-1997)	159,813	Yes	General developmental delay, special education	School readiness

Authors	Reference group	Design	N	Adjusted estimates	Outcomes significant associated	Outcomes not significantly associated
Nepo-mnyaschy (2011)	37-41 weeks	Prospective cohort (U.S., 2001)	5,450	Yes	Poor language scores, poor reading scores, poor math scores	Motor developmental delay, social developmental delay
Petrini (2009)	37-41 weeks	Retrospective cohort (U.S., 2000-2004)	137,296	Yes	General developmental delay, cerebral palsy, seizure disorders	
Poulsen (2013)	39-41 weeks	Retrospective cohort (U.K., 2000-2002)	14,027	Yes	School readiness, poor reading scores	Poor reading scores
Quigley (2012)	39-41 weeks	Prospective cohort (U.K., 2000-2002)	9,523	Yes	Poor language scores, poor reading scores, poor math scores	Motor developmental delay, social developmental delay
Shapiro-Mendoza (2013)	39-41 weeks	Retrospective cohort (U.S., 1998-2005)	554,947	Yes	General developmental delay	
Silva (2006)	37-42 weeks	Prospective cohort (U.K., 1970)	8,779	Yes		Poor language scores, poor reading scores, poor math scores
Talge (2010)	37-41 weeks	Prospective cohort (U.S., 1983-1985)	336	Yes	Overall IQ, non-verbal IQ	Verbal IQ
Williams (2013)	37-41 weeks	Retrospective cohort (U.S., 1998-2003)	314,328	Yes	Poor reading scores, poor math scores	

Authors	Reference group	Design	N	Adjusted estimates	Outcomes significant associated	Outcomes not significantly associated
Woythaler (2011)	≥37 weeks	Prospective cohort (U.S., 2001)	7,500	Yes	General developmental delay, motor developmental delay	

Table 2.5. Summary of Studies Examining Association between Early Term Birth and Poor Developmental Outcomes.

Authors	Reference group	Design	N	Adjusted estimates	Outcomes significant associated	Outcomes not significantly associated
Noble (2012)	41 weeks	Retrospective cohort (U.S., 1988-1992)	128,050	Yes	Poor reading scores, poor math scores	
Poulsen (2013)	39-41 weeks	Retrospective cohort (U.K., 2000-2002)	14,027	Yes		School readiness, poor reading scores, poor math scores
Quigley (2012)	39-41 weeks	Prospective cohort (U.K., 2000-2002)	9,523	Yes	Poor language scores, social developmental delay	Poor math scores, motor developmental delay
Shapiro-Mendoza (2013)	39-41 weeks	Retrospective cohort (U.S., 1998-2005)	554,947	Yes	General developmental delay	
Yang (2010)	39-41 weeks	Randomized trial (B.Y., 1996-1997)	13,643	Yes	Overall IQ (37), non-verbal IQ (37)	Overall IQ (38), verbal IQ, non-verbal IQ (38), poor reading scores, poor math scores

Table 2.6. Previous Consideration of Social Factors.

Authors	Social context: family structure	Social context: family resources	Social context: family functioning	Proximal social processes
Baron (2009)	---	Contr: Maternal education	---	---
Chyi (2008)	---	Contr: Income or employment, maternal education	---	---
Gurka (2010)	---	Contr: Maternal education, maternal age, maternal depression	Contr: Family functioning	---
Harris (2013)	---	Contr: Maternal education	---	---
Linnet (2006)	Contr: Partnership status	Contr: Income or employment, maternal age	---	---
Lipkind (2012)	---	Contr: Income or employment, maternal education, maternal age	---	---
Morse (2009)	Contr: Partnership status	Contr: Maternal education, maternal age	---	---
Moster (2008)	Contr: Partnership status	Contr: Maternal education, maternal age	---	---

Authors	Social context: family structure	Social context: family resources	Social context: family functioning	Proximal social processes
Nepomnyaschy (2011)	Contr: Partnership status	Contr: Income or employment, maternal education, maternal age	---	---
Noble (2012)	Contr: Partnership status	Contr: Income or employment, maternal education, maternal age	---	---
Petrini (2009)	---	---	---	---
Poulsen (2013)	Contr: Partnership status	Contr: Income or employment, maternal age		
Quigley (2012)	Contr: Partnership status	Contr: Maternal education, maternal age	---	---
Shapiro-Mendoza (2013)	---	Contr: Maternal education, maternal age	---	---
Silva (2006)	Contr: Partnership status	Contr: Maternal age	---	---
Talge (2010)	Contr: Partnership status	Contr: Maternal education	---	---
Williams (2013)	---	Contr: Maternal education, maternal age	---	---

Authors	Social context: family structure	Social context: family resources	Social context: family functioning	Proximal social processes
Woythaler (2011)	---	Contr: Income or employment, maternal depression	---	---
Yang (2010)	Contr: Partnership status	Contr: Income or employment, maternal education, maternal age	---	---

Contr: Controlled for.

Chapter 3

Neonatal Outcomes of Late Preterm and Early Term Birth: Roles of Gestational Age and Biological Determinants of Preterm Birth[1]

3.1 Introduction

Preterm birth is defined as delivery prior to 37 weeks gestation. While infants born toward the end of this preterm period were traditionally assumed to be "low risk," recent research has shown increased risk for neonatal morbidity and mortality associated with late preterm birth (34 to 36 weeks) and early term (37 to 38 weeks) birth. However, it is unclear to what extent these risks are associated directly with being born early or with the reasons for preterm birth.

Compared to infants born at term, infants born late preterm are at increased risk for neonatal intensive care unit (**NICU**) admission (1-3) and longer hospital stay during the birth hospitalization (4). They are also at greater risk for respiratory morbidity (1, 4-6), temperature instability (3, 6), hypoglycemia (3, 6), sepsis (1, 2), hyperbilirubinemia (4-6), necrotizing enterocolitis (2), neurological morbidity (1, 2), and even neonatal and infant mortality (7). Typically, the comparison group for infants born late preterm is those born at 37 weeks or later. However, research has shown that the median gestational age is 39 weeks (8). Moreover, infants born at 37 and 38 weeks are at increased risk, compared to their full term peers (39-41 weeks), for NICU admission (9), hospital readmission (10), and longer stay (9, 10); respiratory (9) and other (9, 11, 12) neonatal morbidity; and mortality (13). While some studies failed to find increased risk at 38 weeks (9, 14), the majority of the literature points to the need to examine early term infants as a separate group (15).

Although there is evidence for physiological immaturity in the late preterm and early term periods (16), it is possible that poor neonatal outcomes among infants born late

[1] A version of this section was published elsewhere as, Brown HK, Speechley KN, Macnab J, Natale R, Campbell MK. Neonatal morbidity associated with late preterm and early term birth: The roles of gestational age and biological determinants of preterm birth. Int J Epi. 2013; doi: 10.1093/ije/dyt251.

preterm and early term are associated not only with being born early but also with the reasons for being born early (17). Moreover, in utero exposure to these pathological conditions associated with early birth may even exacerbate the risk of poor neonatal outcomes (18). Previous studies have attempted to address this by examining differences among medically indicated and spontaneous preterm births (19, 20). However, this distinction has limited etiological significance because maternal medical conditions are observed not only in medically indicated preterm birth but also in spontaneous preterm birth (21).

The onset of labour (i.e., physician-initiated or spontaneous) should be considered separately from the presence of maternal medical conditions which contribute to a pathological intrauterine environment regardless of the nature of labour onset. Only a handful of studies have examined the impact of specific maternal medical conditions on neonatal outcomes among infants born late preterm and early term (e.g., (22)). These "biological determinants of preterm birth" can be categorized as infection and inflammation, placental ischemia and other hypoxia, endocrine triggers, and other biological determinants (23, 24). (See Figure 2.2.)

3.1.1 Objectives

The overall aim of this study was to elucidate the role that gestational age plays in determining risk of poor neonatal outcomes among infants born late preterm and early term compared to those born full term by examining the contribution of gestational age to these outcomes within the context of biological determinants of preterm birth. The research questions were as follows:

1. How does the risk of poor neonatal outcomes among infants born late preterm and early term compare to that of infants born full term?

2. Does gestational age act as a partial mediator between biological determinants of preterm birth and poor neonatal outcomes?

3. Do biological determinants of preterm birth modify the effect of gestational age on poor neonatal outcomes?

3.2 Methods

3.2.1 Study Design and Setting

This retrospective cohort study was conducted in London, Canada. Ethics approval was obtained from the University of Western Ontario Health Sciences Research Ethics Board. Two administrative data sources, a city-wide perinatal database and the hospitals' Discharge Abstract Database, were used. These databases collect information on all births occurring at two teaching hospitals in London (a level II hospital and a level III hospital) which together service the needs of a population of approximately 360,000 local residents with more than 5,000 births annually. The study period covered births between April 1, 2002 and March 31, 2011, affording a sample size of 38,807 births for the analyses after exclusions.

The data sources were linked using infant chart number. The accuracy of this linkage was assessed by comparing variables available in both data sources. If there were discrepancies, the infant was excluded from the analysis according to a set of predetermined rules. (See Figure 3.1. and Appendix A.1 for details.)

3.2.2 Participants

Several criteria were used to define the study population: 1) resident of the City of London or Middlesex County (because high risk transfers from outside the region to the level III centre have unique risks for maternal and/or neonatal morbidity); 2) born at 34-41 weeks (because risks associated with very preterm birth are well-established, and post-term deliveries have higher risk for morbidity and mortality than full term deliveries (25)); and 3) singleton gestation (because twins and higher order multiples have differential risks for early delivery (26) and poor neonatal outcomes (27)).

After formulation of the study population, two exclusion criteria were applied to derive the study sample. First, infants with major congenital anomalies were excluded, since major congenital anomalies are associated with both earlier gestational age and with morbidity and mortality (7). (Major congenital anomalies were defined as life-threatening, disabling, or requiring major surgery, including chromosomal trisomies.)

Second, stillbirths and early neonatal deaths were excluded. (Refer to the Limitations section for a discussion of this decision.)

3.2.3 Data Sources

The perinatal database contains information on mothers' socio-demographic characteristics, health during pregnancy, and basic neonatal outcomes. Data for all deliveries of infants ≥20 weeks or ≥500 grams (28) were abstracted from medical records and entered into the database. A comprehensive coding manual, with definitions consistent with the International Classification of Disease (**ICD**), guides the coding and recording of all information. The data arise from clinical activity and are primarily used for clinical audits and research; recording health information in the database is therefore part of hospital protocol. The database was established over 30 years ago and is managed by a team with extensive data collection and management experience.

The Discharge Abstract Database contains diagnostic information on a primary and secondary diagnosis as well as up to 23 additional diagnoses for all infants. Diagnoses are recorded using ICD-10 codes (29). The database was constructed to enable submission of standardized clinical and administrative information on inpatient discharges to the Canadian Institute for Health Information (**CIHI**). Data are put through a series of coding quality checks prior to being sent to CIHI (30).

3.2.4 Measures

Gestational age was based on best obstetrical estimate, as recorded in the perinatal database, using the mother's last menstrual period and first trimester ultrasound. The last menstrual period estimate was used if a first trimester ultrasound estimate was within 4 days of the expected date of delivery; otherwise, the ultrasound estimate was used. (In Canada, very few women do not have a prenatal ultrasound. The first ultrasound is, on average, at 14 weeks gestation, and 66.8% of women receive their first ultrasound prior to 18 weeks (31).) Gestational age was based on completed weeks (i.e., birth at 36 6/7 weeks [259 days] = gestational age of 36 completed weeks) (32). Infants were classified as late preterm (34 to 36 weeks), early term (37 to 38 weeks), or full term (39 to 41

weeks), consistent with U.S. National Institute of Child Health and Human Development definitions (32).

Two outcomes were assessed: NICU triage/admission and neonatal respiratory morbidity. NICU triage/admission was determined from the perinatal database and was used to reflect the overall burden of morbidity necessitating specialized care. Infants who were triaged were those who were evaluated for NICU admission for a serious morbidity but were not admitted. Triage was included in this outcome definition because it was expected that this would capture morbidity that did not meet the criteria for admission but that were important enough to warrant special attention. At the time of data collection, only the level III centre had NICU facilities. At the level II centre, infants requiring specialized care were admitted to the specialized nursery; for these analyses, this was also considered "NICU triage/admission." Information on neonatal respiratory morbidity was obtained from ICD-10 codes (29) in the Discharge Abstract Database and included codes P22.0, P22.1, P22.8, P22.9, P27.1, and P29.3 (i.e., respiratory distress syndrome, transient tachypnea of the newborn, other respiratory distress of the newborn, respiratory distress of the newborn unspecified, bronchopulmonary dysplasia, and persistent pulmonary hypertension, respectively).

Biological determinants of preterm birth were categorized based on conceptualizations used in the previous literature (23, 24) and included: infection and inflammation (i.e., bacterial vaginosis, chorioamnionitis, other intrauterine or systemic infections, and premature rupture of the membranes), placental ischemia and other hypoxia (i.e., preeclampsia, eclampsia, chronic and gestational hypertension, small for gestational age [less than 5^{th} percentile], placenta previa, placental abruption, other bleeding, and vascular disease), and other biological determinants (i.e., pre-existing and gestational diabetes mellitus, polyhydramnios, and oligohydramnios). Each mother was coded according to whether or not she had one or more of the conditions within each category of the biological determinants of preterm birth. In the perinatal database, depression and anxiety are noted on the basis of medication use and not diagnosis. Therefore, endocrine triggers were not included in this analysis because it was impossible to disentangle the effects of depression and anxiety from those of the medications used to treat them (33).

Based on the literature review, several variables were assessed for their roles as confounders. Potential confounders were selected based on the literature review and on the causal thinking used in the conceptual model. Information on all confounders was obtained from the perinatal database. These variables included prenatal socio-demographic and lifestyle variables (i.e., maternal age, maternal marital status, median neighbourhood family income, parity, previous preterm delivery, previous spontaneous or induced abortion, prenatal care, smoking during pregnancy, drug use during pregnancy, and alcohol use during pregnancy); other maternal medical conditions thought to present a risk to the pregnancy (i.e., anemia, autoimmune conditions, connective tissue disorders, hormonal disease [such as polycystic ovaries], gastrointestinal disease, hematological disease, renal disease, and respiratory disease); labour variables (i.e., cord complications, forceps, and vacuum extraction); and additional covariates (i.e., infant sex). (Refer to Appendix A.2 for details.) Non-reassuring fetal heart rate, fetal distress, and labour onset (i.e., caesarean section without labour, induced labour, or spontaneous labour) were not included in the multivariable analyses because they were considered to be on the causal pathway.

3.2.5 Statistical Analyses

SAS 9.2 (34) was used for all analyses. (Refer to Appendix A.4 for analysis details.) Descriptive analyses included frequencies and percentages. Univariable modified Poisson regression (using PROC GENMOD) (35) was used to assess unadjusted associations between the covariates and the outcomes of interest prior to multivariable analyses.

To address the first research question, adjusted relative risks were estimated directly using multivariable modified Poisson regression (35) with generalized estimating equations (**GEE**) (36) to adjust the variance for non-independence due to repeated births to the same mother throughout the study period. Parsimonious models were built using blockwise entry of variables according to the conceptual categories: prenatal socio-demographic and lifestyle variables, biological determinants of preterm birth, other pre-delivery covariates, labour variables, gestational age, and other covariates. To achieve a conservative balance between the dual objectives of eliminating bias and minimizing

variance, a significance level of $p<.20$ was used to retain covariates at each step (37); 95% confidence intervals were used in the final models (38).

To address the second and third research questions, additional analyses were performed on the final multivariable models produced for the first research question. To address research question two, GEE was used to test the significance of the difference in coefficients between full (with gestational age) and reduced (without gestational age) models using methods described by Schluchter (39). This difference in coefficients represents the indirect effect of the biological determinants of preterm birth (i.e., "through" gestational age) (39).

To address research question three, additive interaction was explored by calculating the relative excess risk due to interaction ($RERI = RR_{11} - RR_{10} - RR_{01} + 1$) (40). Confidence intervals were calculated using the MOVER (method of variance estimates recovery) technique (40). (Note that for RERIs, 0 indicates no excess risk.)

3.3 Results

Overall, 39,438 infants were eligible for the study. Of these, 631 (1.6%) were excluded due to discrepancies between the two data sources following linkage. This left a sample of N=38,807 infants. (See Figure 3.1.) Table 3.1 summarizes the descriptive statistics for the sample. In the sample, 4.7% of deliveries were late preterm, 24.8% were early term, and 70.5% were full term.

3.3.1 Research Question One

The overall rate of NICU triage/admission was 6.9% (38.9% in late preterm, 7.7% in early term, and 4.6% in full term infants). After controlling for confounders, infants born late preterm (aRR=6.14, 95% CI 5.63, 6.71) and early term (aRR=1.54, 95% CI 1.41, 1.68) were at increased risk for NICU triage/admission compared to those born full term. (See Table 3.2.)

The overall rate of neonatal respiratory morbidity was 3.5% (17.7% in late preterm, 3.8% in early term, and 2.5% in full term infants). After controlling for confounders, infants

born late preterm (aRR=6.16, 95% CI 5.39, 7.03) and early term (aRR=1.46, 95% CI 1.29, 1.65) were at increased risk for neonatal respiratory morbidity. (See Table 3.3.)

3.3.2 Research Question Two

Gestational age was tested as a partial mediator between the biological determinants of preterm birth and neonatal outcomes. For each outcome, the total, direct, and indirect effects of each biological determinant are shown in Table 3.4. For both NICU triage/admission and neonatal respiratory morbidity, late preterm and early term birth partially mediated the effects of infection and inflammation, placental ischemia and other hypoxia, and other biological determinants on neonatal outcomes.

3.3.3 Research Question Three

Next, additive interactions between gestational age and biological determinants of preterm birth were tested. (See Table 3.5.) For NICU triage/admission, there was no interaction between infection and inflammation and gestational age. There was evidence of excess risk due to interaction for placental ischemia and other hypoxia and late preterm birth as well as early term birth. Similar results were seen for other biological determinants and early term birth. For neonatal respiratory morbidity, there was evidence of excess risk due to interaction for only placental ischemia and other hypoxia and early term birth.

3.3.4 Sensitivity Analyses

The relative risks for the biological determinants of preterm birth and gestational age were only slightly attenuated when fetal distress, non-reassuring fetal heart rate, and labour onset (pathway variables) were added to the multivariable models. (Refer to Appendix A.7.)

3.4 Discussion

These findings show that, consistent with previous research, among infants born late preterm and early term, there is elevated risk for NICU triage/admission (1, 2, 9) and neonatal respiratory morbidity (1, 4-6, 9). These findings add to a growing body of

literature showing that delivery prior to 39 weeks gestation is associated with poor neonatal outcomes.

A unique finding is that this study shows how and when poor outcomes occur in this late preterm and early term population. The mediation analysis showed that a pathological intrauterine environment (characterized by infection and inflammation, placental ischemia and other hypoxia, or other biological determinants) acts through early birth to produce poor outcomes. In other words, gestational age is on the causal pathway between biological determinants of preterm birth and neonatal outcomes. The moderation analysis adds to this by showing that infants who are exposed to both pathological intrauterine conditions and early delivery have excess risk for poor neonatal outcomes. Previous studies have acknowledged that factors leading to early birth could influence the effects of mild prematurity on neonatal outcomes (19, 20). However, the majority of these studies have fallen short of addressing this hypothesis by examining only whether births were medically indicated or spontaneous. By examining the roles of gestational age and groups of biological determinants of preterm birth that share a common pathophysiology, this study provides insight into the "upstream" etiology of neonatal morbidity associated with late preterm and early term birth. The association between infection and inflammation and poor neonatal outcomes may be explained by the ability of pro-inflammatory cytokines to produce a "fetal inflammatory response" (41). Placental ischemia and other hypoxia are characterized by impairment of placental bloodflow, which results in reduced delivery of oxygen and nutrients (42). The mechanisms associated with other biological determinants are less understood; for diabetes mellitus, fetal hyperglycemia and hypoxia may play a role (43).

Moderated mediation (i.e., when a mediator [in this case, gestational age] also interacts with the exposure [in this case, biological determinants of preterm birth]) has been the subject of a considerable amount of theoretical research (44-47). Although there is debate surrounding how to test this phenomenon (i.e., in separate analyses (46), as in this paper, or in a complex, combined analysis (45, 47)), the results of the mediation and moderation analyses in the current study allow one consistent conclusion to be made: the issue of late preterm and early term birth cannot be considered in isolation. One must also consider

the reasons for early birth, which may act through (mediation) and with (moderation) gestational age to produce poor neonatal outcomes.

3.4.1 Strengths and Limitations

A major strength of this study was the ability to link two city-wide data sources. Together, these data sources provided rich and detailed information on pre-existing and pregnancy-related maternal health, on labour and delivery (perinatal database), and on neonatal outcomes (Discharge Abstract Database). Utilization of these data sources also enabled us to capture information on all hospital births in London during the study period, thus ensuring the generalizability of results to the study population. Moreover, the large sample size allowed for an examination of interactions between gestational age and sometimes uncommon biological determinants of preterm birth.

There are several limitations which should be taken into account. As described by Iams (48) in his recent editorial, our study was subject to issues that characterize all retrospective cohort studies, including potential data inaccuracy and unavailability of some variables needed to address the conceptual model. For example, there may have been underestimation of neonatal morbidity due to (for NICU triage/admission) treatment of mild morbidity (e.g., hyperbilirubinemia) in the well-baby nursery or (for neonatal respiratory morbidity) under-documentation of diagnoses in the Discharge Abstract Database (49). Certain covariates (e.g., cord complications) may have also been overestimated. We were also unable to completely address the conceptual model due to inadequate information on endocrine triggers. Study-specific prospective collection of data immediately following events of interest would reduce the occurrence of data inaccuracies and would ensure collection of all variables needed to address the conceptual model.

Also described by Iams (48), our study was limited by the measurement of gestational age and the assumptions behind its interpretation. There may have been non-differential misclassification of gestational age due to “mixing” of adjacent categories (between late preterm and early term or early term and full term). Moreover, we assume that gestational age is an accurate marker of fetal maturity. This may be a limitation if different fetuses

have different levels of functional maturity at a given gestational age. Improvement of measurement of fetal maturity would make findings in future studies more robust.

It should be noted that exclusion of stillbirths and early neonatal deaths from the study sample restricts the scope of the conclusions that can be made; the magnitude of the risks found for the investigated associations is only applicable to survivors. Stillbirths were excluded since the goal of the study was to examine the impacts of both prematurity and the biological determinants of preterm birth. Stillbirth, by definition, is not a possible consequence of prematurity (50). Both stillbirths and neonatal deaths were extremely rare in the study population. Any bias resulting from their exclusion would likely be in the direction of the null. Results remain useful to clinicians, since, at these later gestational ages, they will be mainly concerned with risks of morbidity among survivors.

3.4.2 Future Directions and Implications

Future research could build upon this study by further refining the measurement of biological determinants of preterm birth through re-examination of the model using a dataset with diagnostic information on endocrine triggers and through re-grouping of "other biological determinants" as understanding of the pathophysiology of these conditions improves. Moreover, the inter-relationship between gestational age and biological determinants of preterm birth could be investigated in relation to other neonatal outcomes of importance to late preterm and early term birth (e.g., hypoglycemia, hyperbilirubinemia).

A dramatic increase in preterm birth over the last 20 years has received worldwide attention (51). An increase in the rate of late preterm birth accounts for most of this increase (8). Moreover, elective deliveries in the early term period are becoming more common (15). An understanding of the causes of poor outcomes in these infants is therefore critical. The risks of early delivery should be weighed carefully against the risks of prolonging pregnancy. Although gestational age remains a strong predictor of poor neonatal outcomes even during the late preterm and early term periods, this study shows that biological determinants of preterm birth may act through and with gestational age to produce poor neonatal outcomes.

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Figure 3.1. Study Flowchart.

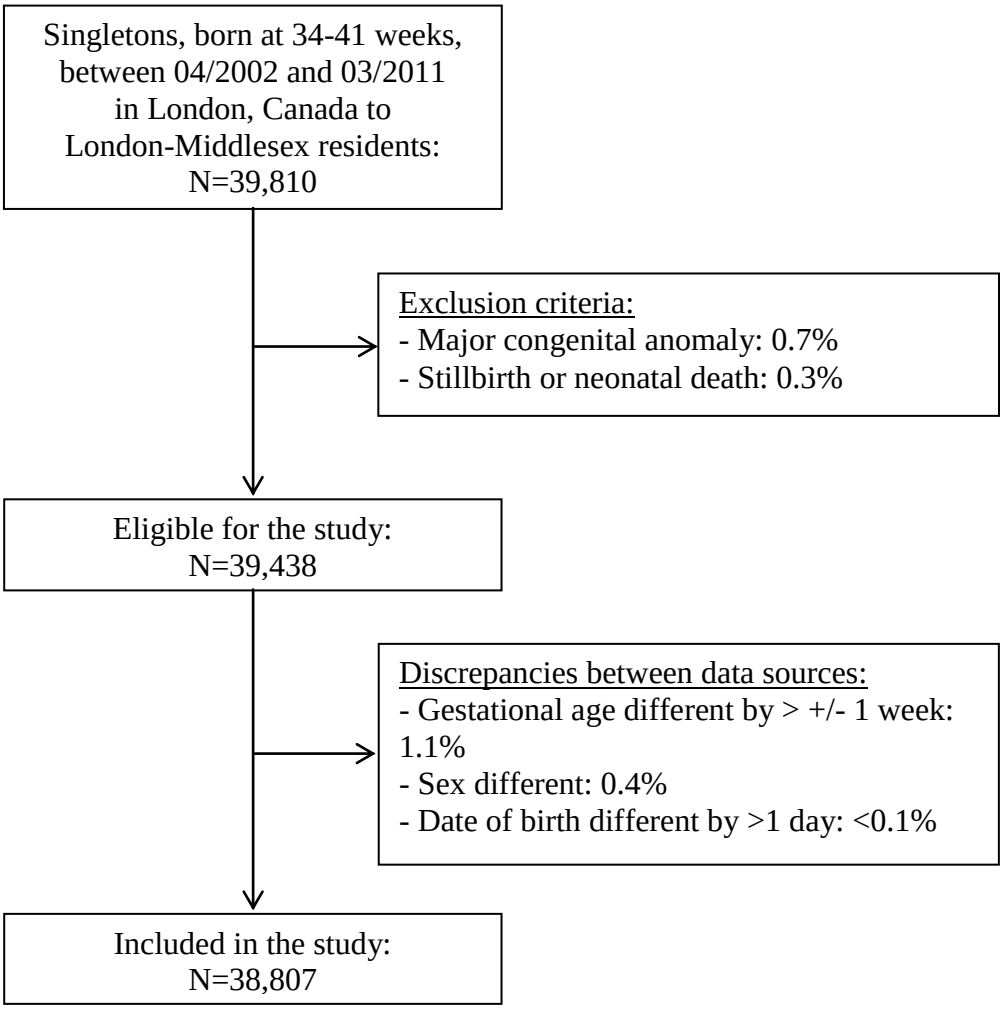

Table 3.1. Sample Characteristics (N=38,807).

	N	%
Prenatal socio-demographic and lifestyle variables		
Maternal age		
<20 years	1,935/38,796	5.0
20-34 years	30,332/38,796	78.2
≥35 years	6,529/38,796	16.8
Maternal marital status		
Single (never married)	5,677/38,135	14.9
Widowed, separated, divorced	468/38,135	1.2
Common-law	5,971/38,135	15.7
Married	26,019/38,135	68.2
Median neighbourhood family income (CAD)		
$50,000-$59,999	8,797/38,807	23.2
$60,000-$69,999	15,174/38,807	39.1
$70,000-$79,999	6,174/38,807	15.9
$80,000-$89,999	5,863/38,807	15.1
$90,000 or more	2,617/38,807	6.7
Parity		
Nulliparous	17,184/38,807	44.3
Primi/multiparous	21,623/38,807	55.7
Previous preterm delivery		
Yes	2,073/38,807	5.3
No	36,734/38,807	94.7
Previous abortion (spontaneous, induced)		
Yes	12,415/38,806	32.0
No	26,391/38,806	68.0
Prenatal care		
None / inadequate (<4 visits at 36 weeks)	558/38,807	1.4
Normal / adequate	38,249/38,807	98.6
Smoking during pregnancy		
Yes	6,492/38,806	16.7
No	32 314/38,806	83.3
Drug use during pregnancy		
Yes	949/38,806	2.4
No	37,857/38,806	97.6
Alcohol during pregnancy		
Yes	622/38,804	1.6
No	38,182/38,804	98.4
Biological determinants of preterm birth		
Infection and inflammation		
Yes	2,811/38,807	7.2
No	35,996/38,807	92.8

	N	%
Placental ischemia and other hypoxia		
Yes	8,098/38,807	20.9
No	30,709/38,807	79.1
Other biological determinants		
Yes	3,116/38,807	8.0
No	35,691/38,807	92.0
Other pre-delivery covariates		
Other maternal medical conditions		
Yes	8,871/38,807	22.6
No	29,936/38,807	77.4
Labour variables		
Cord complications		
Yes	12,073/38,807	31.1
No	26,734/38,807	68.9
Non-reassuring fetal heart rate		
Yes	5,976/38,803	15.4
No	32,827/38,803	84.6
Fetal distress		
Yes	791/38,792	2.0
No	38,001/38,792	98.0
Labour onset		
No labour	3,369/38,805	8.7
Induced labour	14,343/38,805	37.0
Spontaneous labour	21,093/38,805	54.3
Forceps		
Yes	2,932/38,723	7.6
No	35,791/38,723	92.4
Vacuum extraction		
Yes	394/38,803	1.0
No	38,409/38,803	99.0
Gestational age		
Gestational age		
Late preterm	1,838/38,807	4.7
Early term	9,606/38,807	24.8
Full term	27,363/38,807	70.5
Other covariates		
Infant sex		
Male	19,856/38,807	51.2
Female	18,951/38,807	48.8

Table 3.2. Unadjusted and Adjusted Associations between Covariates and NICU Triage/admission.

	% triaged / admitted	Unadjusted RR (95% CI)	Adjusted RR (95% CI)
Prenatal socio-demographic and lifestyle variables			
Maternal age			
<20 years	8.0	1.20 (1.02, 1.40)	0.91 (0.77, 1.07)
20-34 years	6.7	reference	reference
≥35 years	7.5	1.13 (1.02, 1.24)	1.12 (1.02, 1.24)
Maternal marital status			
Single (never married)	8.8	1.38 (1.25, 1.52)	---
Widowed, separated, divorced	7.7	1.21 (0.86, 1.69)	
Common-law	7.2	1.12 (1.01, 1.25)	
Married	6.4	reference	
Median neighbourhood family income			
$50,000-$59,999	7.6	1.14 (0.97, 1.33)	---
$60,000-$69,999	6.9	1.03 (0.88, 1.21)	
$70,000-$79,999	6.5	0.98 (0.82, 1.16)	
$80,000-$89,999	6.1	0.91 (0.76, 1.08)	
$90,000 or more	6.7	reference	
Parity			
Nulliparous	8.1	1.39 (1.29, 1.50)	1.31 (1.22, 1.42)
Primi/multiparous	5.9	reference	reference
Previous preterm delivery			
Yes	9.7	1.45 (1.27, 1.67)	---
No	6.7	reference	
Previous abortion (induced, spontaneous)			
Yes	7.0	1.02 (0.94, 1.10)	---
No	6.8	reference	
Prenatal care			
None / inadequate	19.2	2.87 (2.40, 3.43)	1.59 (1.31, 1.93)
Normal / adequate	6.7	reference	reference
Smoking during pregnancy			
Yes	9.1	1.42 (1.30, 1.55)	1.07 (0.97, 1.18)
No	6.4	reference	reference
Drug use during pregnancy			
Yes	22.0	3.40 (2.99, 3.86)	2.12 (1.82, 2.48)
No	6.5	reference	reference
Alcohol during pregnancy			
Yes	11.4	1.68 (1.35, 2.10)	---
No	6.8	reference	

	% triaged / admitted	Unadjusted RR (95% CI)	Adjusted RR (95% CI)
Biological determinants of preterm birth			
Infection and inflammation			
Yes	16.1	2.62 (2.39, 2.88)	1.90 (1.72, 2.09)
No	6.1	reference	reference
Placental ischemia and other hypoxia			
Yes	11.5	2.02 (1.87, 2.19)	1.50 (1.39, 1.62)
No	5.7	reference	reference
Other biological determinants			
Yes	12.7	1.99 (1.80, 2.21)	1.47 (1.33, 1.62)
No	6.4	reference	reference
Other pre-delivery covariates			
Other maternal medical conditions			
Yes	8.2	1.26 (1.16, 1.37)	1.08 (0.99, 1.17)
No	6.5	reference	reference
Labour variables			
Cord complications			
Yes	7.5	1.13 (1.04, 1.22)	1.09 (1.01, 1.17)
No	6.6	reference	reference
Forceps			
Yes	8.0	1.19 (1.04, 1.35)	---
No	6.8	reference	
Vacuum extraction			
Yes	10.7	1.56 (1.17, 2.08)	1.54 (1.14, 2.07)
No	6.8	reference	reference
Gestational age			
Gestational age			
Late preterm	38.9	8.09 (7.46, 8.77)	6.14 (5.63, 6.71)
Early term	7.7	1.68 (1.54, 1.84)	1.54 (1.41, 1.68)
Full term	4.6	reference	reference
Other covariates			
Infant sex			
Male	7.9	1.37 (1.27, 1.48)	1.31 (1.22, 1.41)
Female	5.8	reference	reference

--- : p>.20 in final model.

Table 3.3. Unadjusted and Adjusted Associations between Covariates and Neonatal Respiratory Morbidity.

	% with resp morb	Unadjusted RR (95% CI)	Adjusted RR (95% CI)
Prenatal socio-demographic and lifestyle variables			
Maternal age			
<20 years	3.7	1.06 (0.84, 1.34)	---
20-34 years	3.5	reference	
≥35 years	3.5	0.99 (0.86, 1.14)	
Maternal marital status			
Single (never married)	4.4	1.36 (1.18, 1.56)	1.15 (1.00, 1.33)
Widowed, separated, divorced	2.8	0.85 (0.49, 1.46)	0.82 (0.48, 1.40)
Common-law	4.0	1.21 (1.05, 1.39)	1.14 (0.99, 1.31)
Married	3.3	reference	reference
Median neighbourhood family income			
$50,000-$59,999	4.0	1.20 (0.95, 1.51)	---
$60,000-$69,999	3.6	1.08 (0.86, 1.35)	
$70,000-$79,999	3.3	1.00 (0.78, 1.29)	
$80,000-$89,999	2.9	0.88 (0.68, 1.13)	
$90,000 or more	3.3	reference	
Parity			
Nulliparous	3.9	1.20 (1.08, 1.33)	1.12 (1.01, 1.25)
Primi/multiparous	3.2	reference	reference
Previous preterm delivery			
Yes	5.6	1.66 (1.38, 1.99)	---
No	3.4	reference	
Previous abortion (induced, spontaneous)			
Yes	3.5	1.00 (0.89, 1.12)	---
No	3.5	reference	
Prenatal care			
None / inadequate	7.5	2.17 (1.62, 2.91)	1.54 (1.12, 2.12)
Normal / adequate	3.5	reference	reference
Smoking during pregnancy			
Yes	3.9	1.14 (1.00, 1.31)	---
No	3.4	reference	
Drug use during pregnancy			
Yes	6.5	1.90 (1.48, 2.43)	1.33 (1.01, 1.74)
No	3.5	reference	reference
Alcohol during pregnancy			
Yes	3.7	1.05 (0.70, 1.57)	0.68 (0.45, 1.04)
No	3.5	reference	reference

	% with resp morb	Unadjusted RR (95% CI)	Adjusted RR (95% CI)
Biological determinants of preterm birth			
Infection and inflammation			
Yes	6.3	1.90 (1.63, 2.22)	1.50 (1.29, 1.75)
No	3.3	reference	reference
Placental ischemia and other hypoxia			
Yes	4.7	1.48 (1.31, 1.66)	1.16 (1.04, 1.31)
No	3.2	reference	reference
Other biological determinants			
Yes	5.3	1.56 (1.33, 1.83)	1.25 (1.07, 1.47)
No	3.4	reference	reference
Other pre-delivery covariates			
Other maternal medical conditions			
Yes	4.0	1.16 (1.03, 1.31)	---
No	3.4	reference	
Labour variables			
Cord complications			
Yes	3.6	1.04 (0.93, 1.16)	---
No	3.5	reference	
Forceps			
Yes	3.8	1.10 (0.91, 1.33)	---
No	3.5	reference	
Vacuum extraction			
Yes	3.8	1.08 (0.66, 1.78)	---
No	3.5	reference	
Gestational age			
Gestational age			
Late preterm	17.7	7.10 (6.27, 8.05)	6.16 (5.39, 7.03)
Early term	3.8	1.51 (1.33, 1.71)	1.46 (1.29, 1.65)
Full term	2.5	reference	reference
Other covariates			
Infant sex			
Male	4.3	1.59 (1.43, 1.77)	1.52 (1.37, 1.69)
Female	2.7	reference	reference

--- : p>.20 in final model.

Table 3.4. Assessment of Partial Mediation of Biological Determinants of Preterm Birth by Gestational Age.

	Values on the logarithmic scale			Indirect effect aRR (95% CI)	% of effect explained by gestational age
	Total effect aβ (95% CI)	Direct effect aβ (95% CI)	Indirect effect[1] aβ (95% CI)		
NICU triage/admission[2]					
Infection and inflammation	0.79 (0.69, 0.88)	0.64 (0.55, 0.74)	0.15 (0.10, 0.19)	1.16 (1.11, 1.21)	18.6
Placental ischemia and other hypoxia	0.59 (0.51, 0.66)	0.41 (0.33, 0.49)	0.18 (0.15, 0.21)	1.19 (1.16, 1.23)	30.2
Other biological determinants	0.58 (0.47, 0.68)	0.39 (0.29, 0.49)	0.19 (0.15, 0.23)	1.21 (1.16, 1.26)	33.0
Neonatal respiratory morbidity[3]					
Infection and inflammation	0.56 (0.41, 0.72)	0.41 (0.25, 0.56)	0.15 (0.11, 0.20)	1.16 (1.12, 1.23)	26.6
Placental ischemia and other hypoxia	0.34 (0.22, 0.46)	0.15 (0.04, 0.27)	0.19 (0.16, 0.22)	1.21 (1.17, 1.25)	54.4
Other biological determinants	0.41 (0.25, 0.57)	0.23 (0.07, 0.39)	0.18 (0.14, 0.22)	1.20 (1.15, 1.25)	45.5

[1] Indirect = total effect – direct effect; indirect effect is equal to G*variable interaction in GEE model assessing mediation (39).
[2] Controls for maternal age, parity, prenatal care, smoking during pregnancy, drug use during pregnancy, other maternal medical conditions, cord complications, vacuum extraction, and infant sex.
[3] Controls for maternal marital status, parity, prenatal care, drug use during pregnancy, alcohol use during pregnancy, and infant sex.

Table 3.5. Assessment of Additive Interaction between Biological Determinants of Preterm Birth and Gestational Age.

Interaction	aRERI (95% CI)[1]
NICU triage/admission[2]	
Infection and inflammation	
and late preterm birth	-0.07 (-1.68, 1.92)
and early term birth	-0.55 (-1.10, 0.65)
Placental ischemia and other hypoxia	
and late preterm birth	2.89 (1.78, 4.08)
and early term birth	0.80 (0.45, 1.16)
Other biological determinants	
and late preterm birth	-0.04 (-1.11, 1.16)
and early term birth	0.44 (0.04, 0.87)
Neonatal respiratory morbidity[3]	
Infection and inflammation	
and late preterm birth	-0.27 (-2.08, 1.92)
and early term birth	-0.30 (-1.03, 0.55)
Placental ischemia and other hypoxia	
and late preterm birth	0.90 (-0.54, 2.44)
and early term birth	0.48 (0.07, 0.92)
Other biological determinants	
and late preterm birth	1.58 (-0.36, 4.01)
and early term birth	0.17 (-0.42, 0.79)

[1] Relative excess risk due to interaction: RERI = $RR_{11} - RR_{10} - RR_{01} + 1$ (Null value = 0) (40).

[2] Controls for maternal age, parity, prenatal care, smoking during pregnancy, drug use during pregnancy, other maternal medical conditions, cord complications, vacuum extraction, and infant sex, as well as the main effects for gestational age and biological determinants of preterm birth.

[3] Controls for maternal marital status, parity, prenatal care, drug use during pregnancy, alcohol use during pregnancy, and infant sex, as well as the main effects for gestational age and biological determinants of preterm birth.

Chapter 4

Developmental Outcomes of Late Preterm and Early Term Birth: Roles of Gestational Age and Proximal Social Processes[2]

4.1 Introduction

Developmental risks associated with very preterm birth (at less than 34 weeks) are well-established (1). Children born closer to term were traditionally assumed to be low risk (2). Recent research suggests that children born late preterm (34 to 36 weeks) and early term (37 to 38 weeks) may be at increased risk for poor developmental outcomes compared to full term peers (39 to 41), prompting some experts to recommend expanding the definition of preterm birth to include all births prior to 39 weeks (3). However, it is unclear to what extent poor outcomes are associated with being born early (physiological immaturity) or with factors associated with being born early (social risk factors).

Studies have shown that, compared to children born at term, children born late preterm are at risk for developmental delay (4) and low IQ (5). They perform worse on academic tests (6-8), are more likely to have special education needs (7, 9), and are at risk for cerebral palsy and attention deficit / hyperactivity disorder (10, 11). A handful of studies have shown that children born early term may be at risk for low IQ (12) and poor academic performance (6) compared to children born full term. On the other hand, several studies failed to find significantly elevated risks for poor developmental outcomes for late preterm (13, 14) and early term (15) birth.

Evidence of rapid fetal brain development between 34 and 40 weeks gestation (16) supports the argument that physiological immaturity explains developmental risks of mild prematurity. However, children do not develop in isolation (17). There is a large body of literature supporting the importance of social factors, particularly parenting, maternal mental health, and family functioning, in child development (17). Nevertheless, most

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previous studies in the late preterm and early term literature have downplayed the role of social factors (e.g., by only controlling for socioeconomic status (7, 9)). The intricacies of the social environment must be taken into account to delineate the effects of late preterm and early term birth on development.

Theories of child development clarify the roles of these social factors. Bronfenbrenner's bioecological theory (18) distinguishes between proximal social processes and social context. Proximal social processes refer to ongoing child-environment interactions; in the early years, the most important is parenting (i.e., interactions, effectiveness, consistency) (19, 20). Social context refers to settings in which the child develops (e.g., home, school, neighbourhood); in the early years, the most important is the home, described by family structure, family resources, and family functioning. The concept of "double jeopardy" enhances bioecological theory by capturing the idea that children with both biological and social risk factors are at even greater risk for poor outcomes compared to those with only biological or only social risk factors (21, 22). The idea was introduced by Escalona, who found greater cognitive decline among low birth weight infants in low versus high socioeconomic households (21). Parenting, a proximal social process, may be a more relevant effect measure modifier since parenting most directly affects child development (23) and parenting, unlike socioeconomic status, is modifiable. (See Figure 2.3.)

4.1.1 Objectives

The overall aim of this study was to elucidate the role that gestational age plays in determining risk of poor developmental outcomes among children born late preterm and early term compared to those born full term by examining the contribution of gestational age to these outcomes within the context of proximal social processes. The research questions were as follows:

1. How does the risk of poor developmental outcomes among children born late preterm and early term compare to that of children born full term?

2. Do proximal social processes modify the effect of gestational age on poor developmental outcomes?

4.2 Methods

4.2.1 Study Design and Setting

This was a secondary analysis of the National Longitudinal Survey of Children and Youth (**NLSCY**), which was conducted by Statistics Canada and followed a sample of Canadian children from 1994/1995 (Cycle 1) to 2008/2009 (Cycle 8). Access to data was obtained through the Social Sciences and Humanities Research Council; ethics approval was not needed since respondents were not identifiable. For this study, 0 to 1 year olds in Early Childhood Development (**ECD**) Cohorts of Cycles 2 through 6 were pooled and followed for two subsequent cycles for a sample size of 15,099 at 2 to 3 years of age and 12,302 at 4 to 5 years of age. (See Figure 4.1 and Appendix B.1 for details.)

4.2.2 Participants

The NLSCY sampling frame excludes children living in institutions or on reserves and those whose parents are members of the Armed Forces. Additional criteria were used to define the study population for this study: 1) born at 34 to 41 weeks (because risks associated with very preterm birth are well-established (1), and post-term deliveries have unique risks (24)); and 2) singleton gestation (because multiple gestations have differential risks for early delivery (25) and poor outcomes (26)).

To define the study sample, children were excluded if their respondent at all cycles was not the biological mother. (Questions about the perinatal period were asked only of biological mothers to maximize validity of responses, and consistency in responses across periods of data collection was important.) At a given cycle, less than 3% of children had a respondent who was not the biological mother. (See Appendix B.1)

4.2.3 Data Sources

The purpose of the NLSCY was to collect information on child health and development and their determinants. Children from all 10 provinces were identified through the Labour Forces Survey, which has a stratified, multistage design that uses probability sampling at each stage. Primary strata were defined by urbanicity; secondary strata were

defined by income and population density. Clusters of dwellings were identified from within strata, and dwellings were systematically sampled from clusters. For ECD Cohorts, one child per household was selected (exception: twins, Cycles 3 and 4). Data collection was by computer-assisted telephone and personal interviewing.

4.2.4 Measures

Gestational age was determined by maternal report (at child age 0 to 1 years) of the number of days or weeks before or after the due date the child was born. Studies generally show accurate maternal recall of gestational age, especially when questions are in relation to due date (versus length of gestation) (27). Nevertheless, to maximize accuracy, children with implausible birth weight for gestational age combinations (i.e., >+/- 4 standard deviations, for males and females separately) were excluded (28, 29). For analysis, gestational age was based on completed weeks (i.e., 36 6/7 weeks = 36 completed weeks) (26) and, consistent with established definitions (2), children were classified as late preterm (34 to 36 weeks), early term (37 to 38 weeks), or full term (39 to 41 weeks) (2).

Developmental outcomes were described in terms of developmental delay and receptive vocabulary delay. Developmental delay was measured at 2 to 3 years of age using the Motor and Social Development Scale (**MSD**), which was developed by the U.S. National Center for Health Statistics based on the Bayley Scales of Infant Development and the Denver Prescreening Developmental Questionnaire (30). The parent responds to 15 yes/no task performance questions (which vary depending on the child's age), and the yes's are summed. Scores were standardized by one-month age groups (M=100, SD=15); children scoring one or more standard deviations below the age-standardized mean were classified as having a delay (32). The MSD has good construct validity; high scores are predictive of fewer behaviour problems (30, 31). Receptive vocabulary delay was measured at 4 to 5 years of age using the Peabody Picture Vocabulary Test-Revised (**PPVT-R**). In the NLSCY, all PPVT-R assessments are conducted in-person with a trained tester who presents a series of pictures and states a word for which the child must choose the correct picture. There are 175 items of increasing difficulty (30). The number

of correct responses is computed, and an age-standardized score is based on one-month age groups. Children scoring one or more standard deviations below the age-standardized mean were classified as having a delay. The PPVT-R performs well, with split-half reliability coefficients around 0.80 (33).

As per the conceptual model, social factors were classified as proximal social processes (i.e., parenting) or social context variables. Parenting was measured using the Parenting Scale. This adaptation of the Parenting Practices Scale (34) assesses patterns of parent-child interactions. Cronbach's alphas for the subscales are: 0.68 (parenting interactions), 0.60-0.63 (parenting effectiveness), 0.65-0.72 (parenting consistency), and 0.52-0.56 (rational parenting; excluded due to poor performance) (30). Questions vary depending on the child's age. (See Appendix B.2.) The Parenting Scale shows good construct validity; it is correlated with family structure and socioeconomic status (30). For each subscale, the standardized average across periods of data collection was taken to reflect the "average exposure" of the child; the "worst" 10% of this standardized average was considered to be the poor parenting group for each subscale. (Averaging measures has the added benefit of producing more reliable estimates.)

Based on the literature review, several variables were assessed as confounders. These included perinatal variables (i.e., smoking during pregnancy, alcohol use during pregnancy, placental ischemia and other hypoxia [maternal hypertension, small for gestational age], other biological determinants [maternal diabetes mellitus], and delivery mode); social context as described by family structure (i.e., maternal partnership status and number of siblings), family resources (i.e., family income adequacy, maternal education, maternal age, maternal health, and maternal mental health), and family functioning; and other covariates (i.e., child sex). (See Appendix B.2 for details.) Neonatal special care and breastfeeding were not included in multivariable analyses because they were considered to be on the causal pathway.

4.2.5 Statistical analyses

SAS 9.3 (35) was used for all analyses. (Refer to Appendix A.4 and Appendix B.4 for analysis details.) Descriptive analyses included frequencies and percentages. Univariable

modified Poisson regression (using PROC GENMOD) (36) was used to assess unadjusted associations between covariates and outcomes prior to multivariable analyses.

To address the first research question, adjusted relative risks were directly estimated using multivariable modified Poisson regression (36). Parsimonious models were built using blockwise entry of variables according to the following conceptual categories: perinatal variables, gestational age, family structure, family resources, family functioning, proximal social processes, and other covariates. A p-value of <.20 was used to retain covariates at each step (37), and 95% confidence intervals were used in the final models (38).

To address the second research question, additive interaction was explored by calculating the relative excess risk due to interaction ($RERI = RR_{11} - RR_{10} - RR_{01} + 1$) (34) for each parenting subscale. Confidence intervals were calculated using the MOVER (method of variance estimates recovery) technique (39). (Note that for RERIs, 0 indicates no excess risk.)

To account for the NLSCY's complex sampling design, longitudinal weights were used for all estimates. (To avoid underestimation of p-values, these weights were normalized to maintain the original sample size (30).) Because statistical packages with bootstrapping capabilities have not yet been developed for modified Poisson regression, the sampling design was taken into account by controlling for province and urban/rural status. Since the dataset included five pooled cycles, a "time" variable was entered into the models to control for cycle of entry into the NLSCY.

4.3 Results

Overall, 18,642 children were eligible for the study. Of these, 0.8% were excluded due to implausible birth weight for gestational age values. By 2 to 3 years, 18.5% of the original sample (N=18,531) had been lost to follow-up or excluded, leaving a sample size of 15,099 children. By 4 to 5 years, 33.6% of the original sample had been lost to follow-up or excluded, for a sample size of 12,302 children. (See Figure 4.1.) Table 4.1 summarizes sample descriptive statistics at both ages.

4.3.1 Research Question One

The overall rate of developmental delay in 2 to 3 year olds was 14.2% (16.7% in late preterm, 14.3% in early term, and 13.9% in full term). In unadjusted analyses, children born late preterm (RR=1.26, 95% CI 1.01, 1.56) appeared to have increased risk for developmental delay. After controlling for confounders, children born late preterm (aRR=1.13, 95% CI 0.90, 1.42) and early term (aRR=1.11, 95% CI 0.96, 1.27) were not at greater risk for developmental delay compared to those born full term. (See Table 4.2.)

The overall rate of receptive vocabulary delay in 4 to 5 year olds was 13.0% (13.1% in late preterm, 13.9% in early term, and 12.7% in full term). After controlling for confounders, children born late preterm (aRR=1.06, 95% CI 0.79, 1.43) and early term (aRR=1.03, 95% CI 0.85, 1.25) were not at greater risk for receptive vocabulary delay compared to those born full term. (See Table 4.3.)

4.3.2 Research Question Two

Additive interactions between gestational age and parenting subscales were tested. (See Table 4.4.) For both outcomes, there was no evidence of excess risk due to interaction for any of the parenting subscales for either late preterm birth or early term birth.

4.3.3 Sensitivity Analyses

Results were unchanged when neonatal special care and breastfeeding (potential pathway variables) were added to the multivariable models. (See Appendix B.7.)

Null findings for research question two could be explained by lack of power due to limiting "poor parenting" to 10% of scores. However, when analyses were re-run using 25% as a cut-off, results remained unchanged, with RERIs near 0. (Data not shown.)

To test the validity of the gestational age variable, we examined the association between late preterm and early term birth and poor neonatal outcomes (40, 41). Compared to children born full term, there was greater risk for neonatal special care for children born late preterm (aRR=3.71, 95% CI 3.15, 4.38) and elevated but not statistically significant risk for children born early term (aRR=1.16, 95% 0.98, 1.37). (See Table 4.5.)

4.4 Discussion

There was elevated risk for developmental delay among children born late preterm compared to those born full term (16.7% vs. 13.3%). While this unadjusted association is an important finding, it was no longer statistically significant in adjusted analyses. Moreover, there was no evidence of increased risk for developmental delay among children born early term or for receptive vocabulary delay among children born late preterm or early term. Although these findings contrast with some previous studies, several others also found no association (13-15).

Despite a null adjusted main effect for gestational age, there could be significant risks associated with late preterm and early term birth in families with important proximal social risks (i.e., poor parenting) (21, 22). This was not the case in our study, in contrast with previous research suggesting an interaction between mild prematurity and social factors (42-44). However, the main effects for parenting showed a strong association with both developmental outcomes, even after controlling for the social context variables. The effects for parenting are consistent with previous literature showing that a lack of positive involvement, punitive discipline because of parenting ineffectiveness, and inconsistency are associated with delayed development (19, 20).

It is important to note that, consistent with previous research (40, 41), we found a strong association between late preterm birth and neonatal special care. This finding gives us confidence of the validity of the gestational age variable available in the NLSCY. This study is one of the first to adequately address the influence of social risk factors when examining the effect of late preterm and early term birth on child development. While previous studies have only controlled for socioeconomic factors (7-9), we were able to take into account both proximal social processes and social context variables. Based on these considerations as well as the null findings shown in several other studies (13-15), it is possible that the impact of mild prematurity loses strength after the neonatal period.

The relative importance, in childhood, of gestational age and parenting is reflected in the size of their relative risks and population attributable fractions (**PAF**s) (45). Relative risks for parenting were larger than those for gestational age. PAFs for parenting

(interactions: 4.3%, 4.2%; effectiveness: 1.4%, 1.3%; consistency: 3.4%, 5.7%) were also generally larger than those for gestational age (late preterm: 1.0%, 0.4%; early term 2.8%, 0.9%) (for developmental delay and receptive vocabulary delay, respectively). These calculations suggest the conclusion that, in births closer to term, the impact of proximal social processes takes precedence over gestational age.

4.4.1 Strengths and Limitations

A major strength of this study is the extensive coverage of information on factors that influence child development. In contrast with previous research (7, 9), we were able to examine parenting and other important social risk factors. Another strength was the use of a nationally representative dataset with longitudinal data. This allowed us to capture aspects of the social environment at more than one time point (e.g., changes in family income adequacy and maternal partnership status over time).

A potential limitation was that NLSCY data were mostly by maternal self-report. Although we took steps to maximize the validity of the gestational age variable, it is possible that null findings could be partially due to misclassification. Other perinatal variables may have been over- or under-reported (46), but this is expected to be minimal since all perinatal questions were asked when the child was 0 to 1 years of age. Likewise, it is possible that maternal report of child outcomes was distorted by the mother's health or socioeconomic characteristics (47). However, parental concerns are considered to be a valuable component of clinical assessments of development (48).

Bias could have been introduced if we falsely considered variables to be mediators or confounders. We did not exclude or control for sensory impairments, disabilities, or chronic health conditions since this could result in "adjusting away" part of the association between gestational age and developmental outcomes (if such conditions are outcomes of mild prematurity). However, because we wanted to isolate the effect of mild prematurity per se, we controlled for biological determinants of early birth (which could harm the fetus) (49) and social factors (which are associated with preterm birth (50) and child development (18)). Although there may be a reciprocal relationship between child behaviour and parenting behaviour (51), we considered parenting to be a confounder

because parenting skills are a proximal representation of the social environment (23). This conceptualization is consistent with previous research (20, 52); moreover, it should be noted that the relationship between gestational age and developmental outcomes was not statistically significant even before parenting was entered into the model. We were unable to exclude children with congenital anomalies, since no question in the NLSCY asks about such conditions. However, congenital anomalies, some of which are not survived past infancy, account for less than 2% of births (53).

This study may be limited by issues related to generalizability. There was loss to follow up; non-respondents were more likely to have social risk factors, including single parent families, income inadequacy, and low maternal education. (See Appendix B.7.) Data collection began before 2000; the incidence of preterm birth has increased in recent years (54), and social conditions have shifted over time. Although it is possible that frequencies of factors under study are not entirely generalizable, our goal was causal inference, not prevalence estimation. According to Rothman (55), threats to external validity do not affect internal validity; therefore, associations are expected to remain valid.

4.4.2 Future Directions and Implications

Future research could build on this study by performing a similar analysis (with full consideration of social factors) in a sample for which there is a prospectively collected measure of gestational age based on first trimester ultrasound (56). There appears to be a dichotomy between clinical samples with gold standard measurement of gestational age (but poor attention to social factors) (11, 12) and population-based surveys with adequate representation of social factors (but only maternal report of gestational age) (4). Although it is difficult to measure all variables with the desired level of precision, there is a need for studies in samples that can adequately address both biological and social factors.

Although there was slightly elevated unadjusted risk of developmental delay associated with late preterm birth, findings from multivariable models suggest that social factors, not gestational age, are the most important predictors of outcomes beyond the neonatal period among births close to full term. For these births, poor parenting may be a more relevant criterion for early intervention eligibility than gestational age.

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Figure 4.1. Study Flowchart.

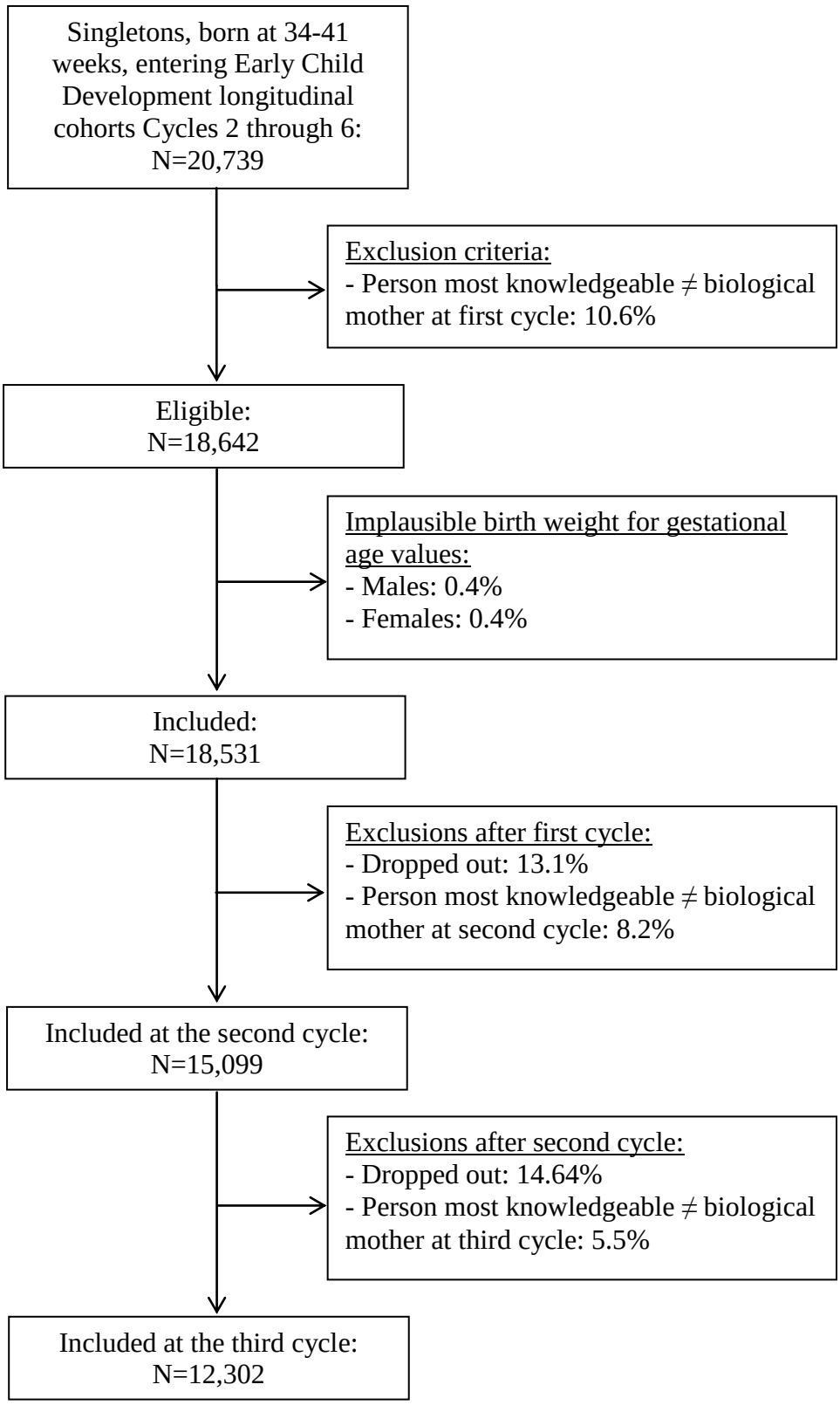

Table 4.1. Weighted Sample Characteristics (N=15,099 at 2-3 years of age; N=12,203 at 4-5 years of age).

	Weighted at 2-3 years		Weighted at 4-5 years	
	N	%	N	%
Perinatal variables				
Smoking during pregnancy				
Yes	2,714.0/14,883.8	18.2	2,226.5/12,150.6	18.3
No	12,169.8/14,883.8	81.8	9,924.1/12,150.6	81.7
Alcohol during pregnancy				
Yes	2,327.1/14,881.2	15.6	1,920.5/12,150.6	15.8
No	12,554.1/14,881.2	84.4	10,230.1/12,150.6	84.2
Placental ischemia and other hypoxia				
Yes	1,872.9/14,883.8	12.6	1,532.8/12,152.0	12.6
No	13,010.9/14,883.8	87.4	10,619.2/12,152.0	87.4
Other biological determinants				
Yes	949.2/14,882.9	6.4	779.3/12,149.8	6.4
No	13,933.7/14,882.9	93.6	11,370.5/12,149.8	93.6
Delivery mode				
Caesarean	2,889.3/15,094.6	19.1	2,354.1/12,298.7	19.1
Vaginal	12,205.3/15,094.6	80.9	9,944.6/12,298.7	80.9
Gestational age				
Gestational age[1]				
Late preterm	1,091.0/15,099.0	7.3	876.8/12,302.0	7.1
Early term	4,338.8/15,099.0	28.7	3,506.2/12,302.0	28.5
Full term	9,669.2/15,099.0	64.0	7,919.0/12,302.0	64.4
Neonatal and infant variables				
Neonatal special care[2]				
Yes	1,283.6/15,092.1	8.5	1,019.3/12,298.3	8.3
No	13,808.5/15,092.1	91.5	11,279.0/12,298.3	91.7
Breastfeeding				
None	2,451.7/14,519.0	16.9	1,966.8/11,825.2	16.6
≤ 6 months	6,617.5/14,519.0	45.6	5,374.6/11,825.2	45.5
> 6 months	5,449.8/14,519.0	37.5	4,483.8/11,825.2	37.9
Social context: family structure				
Maternal partnership status				
Single parent family	1,340.8/15,099.0	8.9	873.9/12,302.0	7.1
Any transition in status	902.6/15,099.0	6.0	1,460.7/12,302.0	11.9
Two parent family	12,855.6/15,099.0	85.1	9,967.4/12,302.0	81.0
Number of siblings				
3 or more	1,086.7/15,099.0	7.2	1,010.1/12,302.0	8.2
1 to 2	10,112.9/15,099.0	67.0	9,316.5/12,302.0	75.7
None	3,899.4/15,099.0	25.8	1,975.4/12,302.0	16.1

	Weighted at 2-3 years		Weighted at 4-5 years	
	N	%	N	%
Social context: family resources				
Family income adequacy				
Any period of inadequacy	2,768.2/15,099.0	18.3	2,466.4/12,302.0	20.0
Consistently adequate	12,330.8/15,099.0	81.7	9,835.6/12,302.0	80.0
Current maternal education				
Secondary or less	4,481.1/14,636.5	30.6	3,743.8/11,692.5	32.0
Some post-secondary	2,688.1/14,636.5	18.4	1,727.4/11,692.5	14.8
College or university degree	7,467.3/14,636.5	51.0	6,211.3/11,692.5	53.2
Maternal age (at birth of child)				
<20 years	568.2/15,099.0	3.8	467.1/12,302.0	3.8
20 years or older	14,530.8/15,099.0	96.2	11,834.9/12,302.0	96.2
Maternal health				
Any period of poor health	1,057.5/14,413.3	7.3	1,206.1/11,623.5	10.4
Consistently good	13,355.8/14,413.3	92.7	10,417.4/11,623.5	89.6
Maternal mental health				
Any period of depression	1,425.3/13,687.6	10.4	1,178.0/10.908.4	10.8
Consistently not depressed	12,262.3/13,687.6	89.6	9,730.4/10,908.4	89.2
Social context variables: other				
Family functioning				
Poor functioning	1,508.4/13,828.4	10.9	1,141.6/10,975.4	10.4
Not poor	12,320.0/13,828.4	89.1	9,833.8/10,975.4	89.6
Proximal social processes				
Parenting interactions				
Negative	1,525.3/14,706.1	10.4	1,313.6/11,864.4	11.1
Positive	13,180.8/14,706.1	89.6	10,550.8/11,864.4	88.9
Parenting effectiveness				
Ineffective	1,316.7/14,490.7	9.1	1,132.6/11,533.4	9.8
Effective	13,174.0/14,490.7	90.9	10,400.8/11,533.4	90.2
Parenting consistency				
Inconsistent	1,323.2/14,279.5	9.3	1,161.7/11,270.3	10.3
Consistent	12,956.3/14,279.5	90.7	10,108.6/11,270.3	89.7
Other covariates				
Child sex				
Male	7,725.7/15,099.0	51.2	6,252.6/12,302.0	50.8
Female	7,373.3/15,099.0	48.8	6,049.4/12,302.0	49.2

[1] Due to exclusions, gestational ages of late preterm, early term, and full term cover 100% of the study sample.
[2] Neonatal special care includes NICU admission, hospital transfer, and use of ventilation.

Table 4.2. Weighted Unadjusted and Adjusted Associations between Covariates and Developmental Delay.

	% with delay	Unadjusted RR (95% CI)	Adjusted RR (95% CI)
Perinatal variables			
Smoking during pregnancy			
Yes	14.9	1.10 (0.95, 1.26)	---
No	13.6	reference	
Alcohol during pregnancy			
Yes	13.7	0.99 (0.84, 1.16)	---
No	13.9	reference	
Placental ischemia and other hypoxia			
Yes	14.6	1.06 (0.89, 1.26)	---
No	13.8	reference	
Other biological determinants			
Yes	15.8	1.15 (0.89, 1.48)	---
No	13.7	reference	
Delivery mode			
Caesarean	16.4	1.24 (1.08, 1.42)	1.19 (1.03, 1.38)
Vaginal	13.3	reference	reference
Gestational age			
Gestational age			
Late preterm	16.7	1.26 (1.01, 1.56)	1.13 (0.90, 1.42)
Early term	14.3	1.07 (0.94, 1.22)	1.11 (0.96, 1.27)
Full term	13.3	reference	reference
Social context variables: family structure			
Maternal partnership status			
Single parent family	14.4	1.04 (0.83, 1.29)	---
Any transition in status	12.6	0.91 (0.70, 1.18)	
Two parent family	13.9	reference	
Number of siblings			
3 or more	17.3	1.48 (1.20, 1.83)	1.36 (1.07, 1.73)
1 to 2	14.4	1.24 (1.07, 1.43)	1.18 (1.00, 1.38)
None	11.6	reference	reference
Social context variables: family resources			
Family income adequacy			
Any period of inadequacy	16.2	1.22 (1.05, 1.41)	1.15 (0.97, 1.36)
Consistently adequate	13.3	reference	reference
Current maternal education			
Secondary or less	16.8	1.34 (1.18, 1.54)	1.27 (1.09, 1.47)
Some post-secondary	12.1	0.97 (0.82, 1.15)	0.96 (0.80, 1.15)
College or university degree	12.5	reference	reference
Maternal age (at birth of child)			
<20 years	13.0	0.94 (0.67, 1.30)	---
20 years or older	13.9	reference	

	% with delay	Unadjusted RR (95% CI)	Adjusted RR (95% CI)
Maternal health			
Any period of poor health	14.5	1.04 (0.86, 1.27)	---
Consistently good	13.9	reference	
Maternal mental health			
Any period of depression	18.0	1.34 (1.12, 1.61)	1.17 (0.96, 1.43)
Consistently not depressed	13.4	reference	reference
Social context variables: other			
Family functioning			
Poor functioning	16.4	1.21 (1.02, 1.44)	---
Not poor	13.5	reference	
Proximal social processes			
Parenting interactions			
Negative	21.1	1.63 (1.39, 1.91)	1.40 (1.17, 1.67)
Positive	13.0	reference	reference
Parenting effectiveness			
Ineffective	16.4	1.22 (1.02, 1.46)	1.14 (0.95, 1.37)
Effective	13.4	reference	reference
Parenting consistency			
Inconsistent	20.2	1.55 (1.29, 1.87)	1.32 (1.08, 1.62)
Consistent	13.1	reference	reference
Other covariates			
Child sex			
Male	19.0	2.25 (1.98, 2.56)	2.36 (2.04, 2.72)
Female	8.4	reference	reference

--- : p>.20 in final model.

* Analyses also control for design variables (cycle of entry into NLSCY, province, and urban/rural status).

Table 4.3. Weighted Unadjusted and Adjusted Associations between Covariates and Receptive Vocabulary Delay.

	% with delay	Unadjusted RR (95% CI)	Adjusted RR (95% CI)
Perinatal variables			
Smoking during pregnancy			
Yes	14.4	1.13 (0.93, 1.36)	---
No	12.8	reference	
Alcohol during pregnancy[1]			
Yes	8.4	0.60 (0.46, 0.77)	0.60 (0.46, 0.78)
No	14.0	reference	reference
Placental ischemia and other hypoxia			
Yes	17.1	1.37 (1.12, 1.69)	1.24 (0.99, 1.53)
No	12.5	reference	reference
Other biological determinants			
Yes	20.9	1.67 (1.30, 2.15)	1.42 (1.07, 1.89)
No	12.5	reference	reference
Delivery mode			
Caesarean	13.2	1.01 (0.84, 1.22)	---
Vaginal	13.0	reference	
Gestational age			
Gestational age			
Late preterm	13.1	1.03 (0.79, 1.35)	1.06 (0.79, 1.43)
Early term	13.9	1.09 (0.91, 1.31)	1.03 (0.85, 1.25)
Full term	12.7	reference	reference
Social context variables: family structure			
Maternal partnership status			
Single parent family	21.1	1.01 (0.73, 1.41)	---
Any transition in status	16.2	1.18 (0.80, 1.74)	
Two parent family	11.9	reference	
Number of siblings			
3 or more	20.2	1.62 (1.24, 2.10)	1.81 (1.30, 2.51)
1 to 2	12.4	0.99 (0.80, 1.22)	1.05 (0.82, 1.35)
None	12.5	reference	reference
Social context variables: family resources			
Family income adequacy			
Any period of inadequacy	24.5	2.35 (2.01, 2.77)	1.60 (1.29, 1.97)
Consistently adequate	10.4	reference	reference
Current maternal education			
Secondary or less	19.4	2.11 (1.78, 2.50)	1.47 (1.20, 1.81)
Some post-secondary	12.4	1.34 (1.05, 1.71)	1.18 (0.92, 1.52)
College or university degree	9.2	reference	reference
Maternal age (at birth of child)			
<20 years	20.3	1.59 (1.20, 2.11)	---
20 years or older	12.8	reference	

	% with delay	Unadjusted RR (95% CI)	Adjusted RR (95% CI)
Maternal health			
Any period of poor health	21.9	1.93 (1.56, 2.40)	1.36 (1.06, 1.74)
Consistently good	11.4	reference	reference
Maternal mental health			
Any period of depression	21.5	1.99 (1.61, 2.45)	1.26 (0.98, 1.64)
Consistently not depressed	10.8	reference	reference
Social context variables: other			
Family functioning			
Poor functioning	19.3	1.71 (1.38, 2.11)	1.32 (1.03, 1.68)
Not poor	11.3	reference	reference
Proximal social processes			
Parenting interactions			
Negative	20.3	1.72 (1.40, 2.13)	1.30 (1.03, 1.64)
Positive	11.8	reference	reference
Parenting effectiveness			
Ineffective	14.6	1.17 (0.93, 1.48)	1.13 (0.88, 1.45)
Effective	12.4	reference	reference
Parenting consistency			
Inconsistent	21.8	1.85 (1.53, 2.24)	1.51 (1.21, 1.87)
Consistent	11.8	reference	reference
Other covariates			
Child sex			
Male	14. 9	1.33 (1.14, 1.56)	1.51 (1.26, 1.79)
Female	11.2	reference	reference

--- : p>.20 in final model.

* Analyses also control for design variables (cycle of entry into NLSCY, province, and urban/rural status).

[1] Alcohol consumption during pregnancy referred to “any” alcohol consumption (since heavy consumption was too rare to be analyzed. As a result, this variable was strongly confounded by high socioeconomic status, which could explain the protective effect seen here.

Table 4.4. Assessment of Additive Interaction between Gestational Age and Proximal Social Processes.

	aRERI (95% CI)[1]
Developmental delay at 2-3 years[2]	
Parenting interactions	
and late preterm birth	-0.33 (-1.09, 0.79)
and early term birth	0.00 (-0.54, 0.59)
Parenting effectiveness	
and late preterm birth	-0.02 (-0.73, 1.23)
and early term birth	-0.20 (-0.68, 0.30)
Parenting consistency	
and late preterm birth	0.09 (-0.77, 1.41)
and early term birth	-0.13 (-0.72, 0.52)
Receptive vocabulary delay at 4-5 years[3]	
Parenting interactions	
and late preterm birth	-1.01 (-1.84, 0.19)
and early term birth	-0.25 (-0.90, 0.39)
Parenting effectiveness	
and late preterm birth	0.13 (-0.91, 2.14)
and early term birth	0.06 (-0.55, 0.78)
Parenting consistency	
and late preterm birth	-0.77 (-1.65, 0.41)
and early term birth	0.06 (-0.62, 0.82)

[1] Relative excess risk due to interaction: $RERI = RR_{11} - RR_{10} - RR_{01} + 1$ (Null value = 0) (38).

[2] Controls for delivery mode, number of siblings, family income adequacy, current maternal education, maternal mental health, child sex, cycle of entry into NLSCY, province, and urban/rural status as well as main effects for gestational age, parenting interactions, parenting effectiveness, and parenting consistency.

[3] Controls for alcohol during pregnancy, placental ischemia and other hypoxia, other biological determinants, number of siblings, family income adequacy, current maternal education, maternal health, maternal mental health, family functioning, child sex, cycle of entry into NLSCY, province, and urban/rural status as well as main effects for gestational age, parenting interactions, parenting effectiveness, and parenting consistency.

Table 4.5. Weighted Unadjusted and Adjusted Associations between Covariates and Neonatal Special Care.

	% with special care	Unadjusted RR (95% CI)	Adjusted RR (95% CI)
Prenatal socio-demographic and lifestyle variables			
Maternal age			
<20 years	10.3	1.21 (0.88, 1.67)	1.14 (0.83, 1.58)
20-34 years	8.5	reference	reference
35 years or more	8.0	0.93 (0.76, 1.14)	0.88 (0.72, 1.11)
Smoking during pregnancy			
Yes	10.2	1.25 (1.05, 1.49)	1.17 (0.98, 1.40)
No	8.2	reference	reference
Alcohol during pregnancy			
Yes	7.5	0.86 (0.68, 1.09)	0.96 (0.76, 1.21)
No	8.7	reference	reference
Biological determinants of preterm birth			
Placental ischemia and other hypoxia			
Yes	14.3	1.86 (1.57, 2.21)	1.59 (1.34, 1.88)
No	7.7	reference	reference
Other biological determinants			
Yes	14.1	1.74 (1.37, 2.20)	1.48 (1.19, 1.83)
No	8.1	reference	reference
Gestational age			
Gestational age			
Late preterm	26.9	4.03 (3.41, 4.75)	3.71 (3.15, 4.38)
Early term	8.0	1.19 (1.01, 1.41)	1.16 (0.98, 1.37)
Full term	6.7	reference	reference
Other covariates			
Child sex			
Male	9.7	1.35 (1.17, 1.55)	1.28 (1.12, 1.47)
Female	7.2	reference	reference

Note: This analysis was conducted in the sample available at 2-3 years of age (N=15,099); results were similar when restricted to the sample available at 4-5 years of age (N=12,302) (data not shown).

* Analyses also control for design variables (cycle of entry into NLSCY, province, and urban/rural status).

Chapter 5

Biological Determinants of Spontaneous Late Preterm and Early Term Birth[3]

5.1 Introduction

Spontaneous preterm labour (i.e., at less than 37 weeks gestation) was traditionally viewed as being fundamentally the same process as spontaneous labour at term, except that it occurred at an earlier gestational age (1). However, although the physiological, biochemical, and clinical components of the final common pathway to parturition are the same (i.e., increased myometrial contractility, cervical ripening/dilation and effacement, and membrane/decidual activation (1)), the nature of the activation of this pathway differs earlier in gestation compared to at term (2). In a healthy term pregnancy, the final common pathway is set in motion in a synchronous manner when the inherent limit of human gestation is reached (i.e., when the mother/placenta can no longer sustain fetal growth). In contrast, preterm parturition is a consequence of multiple pathological signals that trigger one or more of the components of the pathway (2). These pathological signals are heterogeneous, each with a distinct biological mechanism (2).

In one of the most widely cited models of spontaneous preterm labour, Romero et al. (3) described the "preterm parturition syndrome" as including infection, ischemia, endocrine disorders, uterine overdistension, cervical disease, abnormal allograft reaction, and allergic phenomena. In line with this model and others similar to it (4, 5), the focus of most previous etiological studies has been on very preterm birth (at less than 34 weeks) or preterm birth in general (at less than 37 weeks) (6-8).

Growing recognition of the neonatal risks associated with late preterm (34 to 36 weeks) (9) and even early term (37 to 38 weeks) (10) birth has prompted some experts to recommend expanding the definition of "preterm" to include all births prior to 39 weeks

[3] A version of this section was submitted for publication elsewhere as, Brown HK, Speechley KN, Macnab J, Natale R, Campbell MK. Biological determinants of spontaneous late preterm and early term birth: A retrospective cohort study. Br J Obstet Gynaecol. Submitted.

(11). This recommendation points to the need to understand the determinants of "early" birth closer to full term (39 to 41 weeks).

We developed a conceptualization of these "biological determinants of preterm birth" which is based on previous etiological models (4, 5, 12, 13) and is expanded to include additional determinants more relevant to delivery closer to full term (e.g., diabetes mellitus). These biological determinants of preterm birth, grouped according to common hypothesized pathophysiological mechanisms, include infection and inflammation (i.e., chorioamnionitis, bacterial vaginosis, other intrauterine or systemic infection, and premature rupture of the membranes), placental ischemia and other hypoxia (i.e., preeclampsia, eclampsia, chronic and gestational hypertension, fetal growth restriction, placenta previa, placental abruption, other bleeding, and vascular disease), endocrine triggers (i.e., depression, anxiety, and stress), and other biological determinants (i.e., pre-existing and gestational diabetes mellitus, polyhydramnios, and oligohydramnios).

The pathophysiological mechanisms by which infection and inflammation trigger spontaneous preterm labour are perhaps best understood. The detection of foreign microorganisms triggers the release of pro-inflammatory cytokines (e.g., IL-1, tumour necrosis factor). These cytokines stimulate the production of prostaglandins which, in turn, stimulate uterine contractility or degradation of the extracellular matrix of the fetal membranes, thus triggering spontaneous labour (3). The precise mechanism by which placental ischemia and other hypoxia trigger spontaneous preterm labour is unknown; however, when ischemia leads to decidual necrosis and hemorrhage, thrombin (a coagulation factor) may activate the common pathway to parturition (12). Endocrine triggers are also more poorly understood; however, there is a role for corticotrophin-releasing hormone and activation of the maternal or fetal hypothalamic-pituitary-adrenal axis (14, 15). Finally, there are other biological determinants of preterm birth which are more difficult to categorize but which also play an important role in the onset of spontaneous preterm labour. Polyhyramnios and oligohydramnios may lead to spontaneous preterm labour through a signal initiated by the mechanical stretch of the myometrial, cervical, and fetal membranes through the cellular cytoskeleton. This activates cellular protein kinases such that the increase in intrauterine volume exceeds the

ability of the uterus to handle the change (3). Pre-existing and gestational diabetes mellitus have also been associated with spontaneous preterm labour (16, 17).

5.1.1 Objective

The objective of this study was to examine how biological determinants of preterm birth, grouped according to common hypothesized pathophysiological mechanisms, contribute to spontaneous early birth of singletons during the late preterm and early term periods. The biological determinants of preterm birth that were examined included infection and inflammation, placental ischemia and other hypoxia, and other biological determinants of preterm birth (i.e., pre-existing and gestational diabetes mellitus, polyhydramnios, and oligohydramnios).

5.2 Methods

5.2.1 Study Design and Setting

This retrospective cohort study was carried out in London, Canada. Ethics approval was obtained from the University of Western Ontario Health Sciences Research Ethics Board. Data were obtained from a city-wide perinatal database which collects information on all births occurring at two teaching hospitals (a level II hospital and a level III hospital). These hospitals serve the needs of over 360,000 local residents and over 5,000 births per year. The study period covered births between April 1, 2002 and March 31, 2011, and the sample consisted of 17,678 births. (See Figure 5.1.)

5.2.2 Participants

Several criteria were used to define the study population: 1) resident of the City of London or Middlesex County (because high risk transfers to the level III centre have unique risks for maternal morbidity and/or early delivery); 2) born at 34 to 41 weeks (because the focus was on late preterm and early term birth, not very preterm birth); 3) singleton gestation (because multiple gestations have differential risks for early birth (18)); and 4) delivered following spontaneous labour (because the nature of associations for medically indicated births may be different than those for spontaneous births (19)).

Stillbirths (N=20) were excluded because it was not possible to determine gestational age at death.

5.2.3 Data Sources

The perinatal database includes information on mothers' socio-demographic characteristics, pre-existing and pregnancy-related health conditions, and labour and delivery variables. Data for all births ≥20 weeks or ≥500 grams were abstracted from medical records and entered into the database. The database, which was established over 30 years ago, is managed by a team with extensive data collection and management experience. Recording health information in the database is part of hospital protocol; data are a consequence of clinical activity and are used mostly for clinical audits and research.

5.2.4 Measures

Biological determinants of preterm birth were conceptualized based on definitions used in the literature (4, 5, 12, 13): infection and inflammation (i.e., chorioamnionitis, bacterial vaginosis, other intrauterine or systemic infection, and premature rupture of the membranes), placental ischemia and other hypoxia (i.e., preeclampsia, eclampsia, chronic and gestational hypertension, small for gestational age [less than 5^{th} percentile], placenta previa, placental abruption, other bleeding, and vascular disease), and other biological determinants (i.e., pre-existing and gestational diabetes mellitus, polyhydramnios, and oligohydramnios). A biological determinant of preterm birth was said to be present if the mother had one or more of the conditions in a given category. In the perinatal database, endocrine triggers are recorded on the basis of medication use and not diagnosis. Therefore, because it was not possible to disentangle the effects of the conditions from the medications used to treat them (20), endocrine triggers were excluded.

Gestational age was based on best obstetrical estimate using mother's last menstrual period and first trimester ultrasound. The last menstrual period estimate was used unless there was a 4 or more day difference from the first trimester ultrasound estimate; in this case, the ultrasound estimate was used. In Canada, the majority of women (more than 99%) have a prenatal ultrasound, and, among those, 66.8% have their first ultrasound

prior to 18 weeks (21). Gestational age was based on completed weeks (i.e., birth at 36 6/7 weeks = 36 completed weeks) (22). Consistent with U.S. National Institute of Child Health and Human Development definitions (22), infants were classified as late preterm (34 to 36 weeks), early term (37 to 38 weeks), or full term (39 to 41 weeks).

Based on a review of the literature, several variables were controlled for as confounders: prenatal socio-demographic and lifestyle variables (i.e., maternal age, maternal marital status, median neighbourhood income, parity, previous preterm delivery, previous spontaneous or induced abortion, prenatal care, smoking during pregnancy, drug use during pregnancy, and alcohol use during pregnancy) and other pre-delivery covariates (i.e., maternal medical conditions thought to present a risk to the pregnancy [anemia, autoimmune conditions, connective tissue disorders, hormonal diseases such as polycystic ovaries, gastrointestinal disease, hematological disease, renal disease, and respiratory disease]; minor and major congenital anomalies; and fetal sex). (See Appendix A.2.) We did not control for non-reassuring fetal heart rate or fetal distress because these were assumed to be a function of labour, not a determinant of it.

5.2.5 Analysis

To avoid underestimation of the standard error due to clustering of births to the same mother throughout the study period (23), one birth per mother was randomly selected for analysis. SAS 9.2 was used for all analyses (24). (Refer to Appendix A.4 for analysis details.) Descriptive analyses included frequencies and percentages to describe the sample. Multinomial logistic regression was performed using PROC LOGISTIC with a generalized logit link function. Multinomial regression allows for the estimation of models where the outcome has more than two categories (25); in this case, we were able to estimate the odds of both late preterm birth and early term birth relative to full term birth. Parsimonious models were built using blockwise entry of variables according to conceptual categories defined by temporality: prenatal socio-demographic and lifestyle variables, biological determinants of preterm birth, and other pre-delivery covariates. A p-value of .20 was used to retain covariates at each step (26), and 95% confidence intervals were used in the final models (27).

5.3 Results

Overall, 21,546 births were eligible for the study. Of these, 3,868 (18.0%) were excluded to limit the sample to one birth per mother. This left 17,678 spontaneous live births. (See Figure 5.1.) Table 5.1 summarizes the descriptive statistics for the sample. In the sample, 6.3% of births were exposed to infection and inflammation, 16.0% to placental ischemia and other hypoxia, and 3.9% to other biological determinants.

The overall rates of spontaneous late preterm and early term birth were 5.3% and 22.6%, respectively. The rates of spontaneous late preterm and early term birth following exposure to infection and inflammation were 11.0% and 19.7%. After controlling for confounders, infants who had been exposed to infection and inflammation were more likely than those not exposed to be born late preterm (aOR=2.07, 95% CI 1.65, 2.60). There was no evidence of increased odds of early term birth associated with infection and inflammation.

The rates of spontaneous late preterm and early term birth following exposure to placental ischemia and other hypoxia were 9.6% and 25.7%, respectively. After controlling for confounders, infants who had been exposed to placental ischemia and other hypoxia were more likely than those not exposed to be born late preterm (aOR=2.21, 95% CI 1.88, 2.61) and early term (aOR=1.25, 95% CI 1.13, 1.39).

The rates of spontaneous late preterm and early term birth following exposure to other biological determinants (i.e., pre-existing and gestational diabetes mellitus, polyhydramnios, and oligohydramnios) were 13.6% and 38.2%, respectively. After controlling for confounders, infants who had been exposed to other biological determinants of preterm birth were more likely than those not exposed to be born late preterm (aOR=3.61, 95% CI 2.77, 4.69) and early term (aOR=2.52, 95% CI 2.12, 3.00). (Refer to Table 5.2.)

5.4 Discussion

These findings show that infection and inflammation, placental ischemia and other hypoxia, and other biological determinants are important determinants of spontaneous

late preterm and early term birth. These results add to a growing body of literature suggesting that spontaneous preterm birth is caused by multiple pathological mechanisms that trigger the final common pathway to parturition (2). Our study is unique in that we focused on determinants of late preterm and early term birth, thus addressing an important gap in the literature regarding causes of spontaneous birth closer to full term.

A finding of particular importance is that placental ischemia and other hypoxia and other biological determinants of preterm birth (i.e., diabetes mellitus, uterine overdistension) were associated with spontaneous birth even at 37 and 38 weeks. Although the pathological nature of the causes of preterm labour are recognized, the conventional cut-off of 37 weeks in the definition of preterm birth has led to implicit assumptions of (a) healthy outcomes for infants born after 37 weeks and (b) innocuous determinants of spontaneous labour during this period. Research is now beginning to show that infants born early term may be at greater risk than was previously thought for poor neonatal outcomes, including morbidity and even mortality (10). Our study shows that the determinants of spontaneous birth during this period may also be pathological. This finding adds strength to the recommendation that preterm birth be defined as delivery before 39 rather than 37 weeks (11).

If the processes that trigger spontaneous labour prior to full term are pathological, it is plausible that these same processes have implications for fetal and neonatal health. For pregnancies affected by infection and inflammation, pro-inflammatory cytokines can cross the blood-brain barrier and cause a fetal inflammatory response (28) that is reflected in increased risk for neonatal respiratory morbidity and sepsis (29, 30). Placental ischemia and other hypoxia may result in placental vascular lesions (in the case of preeclampsia and placental abruption) (31) or placental insufficiency (due to suboptimal implantation, in the case of placenta previa) (32) that cause impaired oxygen and glucose delivery to the fetus. Consistent with this, studies have shown associations with composite measures of neonatal morbidity as well as neonatal respiratory morbidity (30). Pre-existing and gestational diabetes mellitus may result in maternal or fetal hyperglycemia and hypoxia (17) and have been found to be associated with low Apgar scores (17) and NICU admission (33). Polyhydramnios and oligohydramnios have also

been associated with low Apgar scores (34) and NICU admission (35). Our study shows that spontaneous late preterm and early term birth may result from pathological determinants; these determinants suggest avenues to poor outcomes in infants born close to full term. The finding of pathological determinants of preterm birth associated with spontaneous late preterm and early term birth suggests the need for surveillance of infants born following spontaneous labour and not just medically indicated delivery.

5.4.1 Strengths and Limitations

A strength of this study was the use of a perinatal database that provided detailed information on pre-existing and pregnancy-related maternal conditions. Utilization of this dataset also enabled us to capture information on all hospital births in the region during the study period; this ensures the generalizability of our results to the study population.

There are several limitations that should be acknowledged. We were unable to measure the influence of endocrine triggers (e.g., depression and anxiety) because information on these conditions was only available in the database on the basis of medication use and not diagnosis (20). Moreover, although the use of last menstrual period dating confirmed by first trimester ultrasound is the gold standard for measuring gestational age (36), misclassification of this variable remains a possibility. Such misclassification would likely occur in the form of "mixing" of adjacent categories (late preterm/early term or early term/full term), which could be non-differential (due to digit preference) or differential (due to bias in recording based on health status at birth).

5.4.2 Future Directions and Implications

The association between biological determinants of preterm birth and spontaneous late preterm and early term birth should be tested again with the addition of endocrine triggers from a data source that has the ability to measure diagnosis specifically. Examining the role of these endocrine triggers could provide greater insight into determinants of spontaneous late preterm and early term birth (15). Moreover, future research should examine conditions included in the "other biological determinants" category to determine whether more specific classifications, based on a common pathophysiology, can be made

and explored. The associations between these biological determinants of preterm birth and medically indicated late preterm and early term birth should also be explored. This is critical since many of these biological determinants of preterm birth may also be cause for physician intervention (19, 37) and, in contrast with very preterm birth, medically indicated delivery later in gestation is common (38).

A greater understanding of the etiology of spontaneous late preterm and early term birth has implications for clinical practice. Our finding of multiple pathological etiologies associated with spontaneous late preterm and early term birth adds evidence to the need to develop targeted interventions aimed at specific conditions (rather than preterm birth as a whole) to prevent early birth (38). Preventative measures even later in gestation are important since several studies have shown that 34 to 36 weeks is an important period for fetal development (39, 40), and fetal maturation is a continuous process with no threshold (41). However, although gestation should be prolonged where possible, it is important to acknowledge that many risk factors studied here are not easily modifiable, and preterm birth sometimes does have survival value when the alternative is longer exposure to an increasingly adverse intrauterine environment (42, 43).

Our findings have implications for understanding the risks of morbidity associated with late preterm and early term birth (9, 10). If the processes that trigger spontaneous labour at these gestational ages are pathological and if these processes have implications for fetal well-being, it is likely that some of the morbidity associated with late preterm and early term birth is due not only to prematurity but also to the reasons for preterm birth.

Since 1995, the incidence of preterm birth has risen by 17% and, as of 2004, preterm birth accounted for 8.2% of all births in Canada (44). An increase in the number of late preterm births is responsible for much of this increase, and late preterm births now represent nearly 75% of preterm births (45). Moreover, early term births account for approximately 17.5% of births (46). Because late preterm and early term births represent such a large proportion of live births, understanding the causes of delivery at these gestational ages is critical. Our study provides clues about the biological determinants of spontaneous late preterm and early term birth.

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Figure 5.1. Study Flowchart.

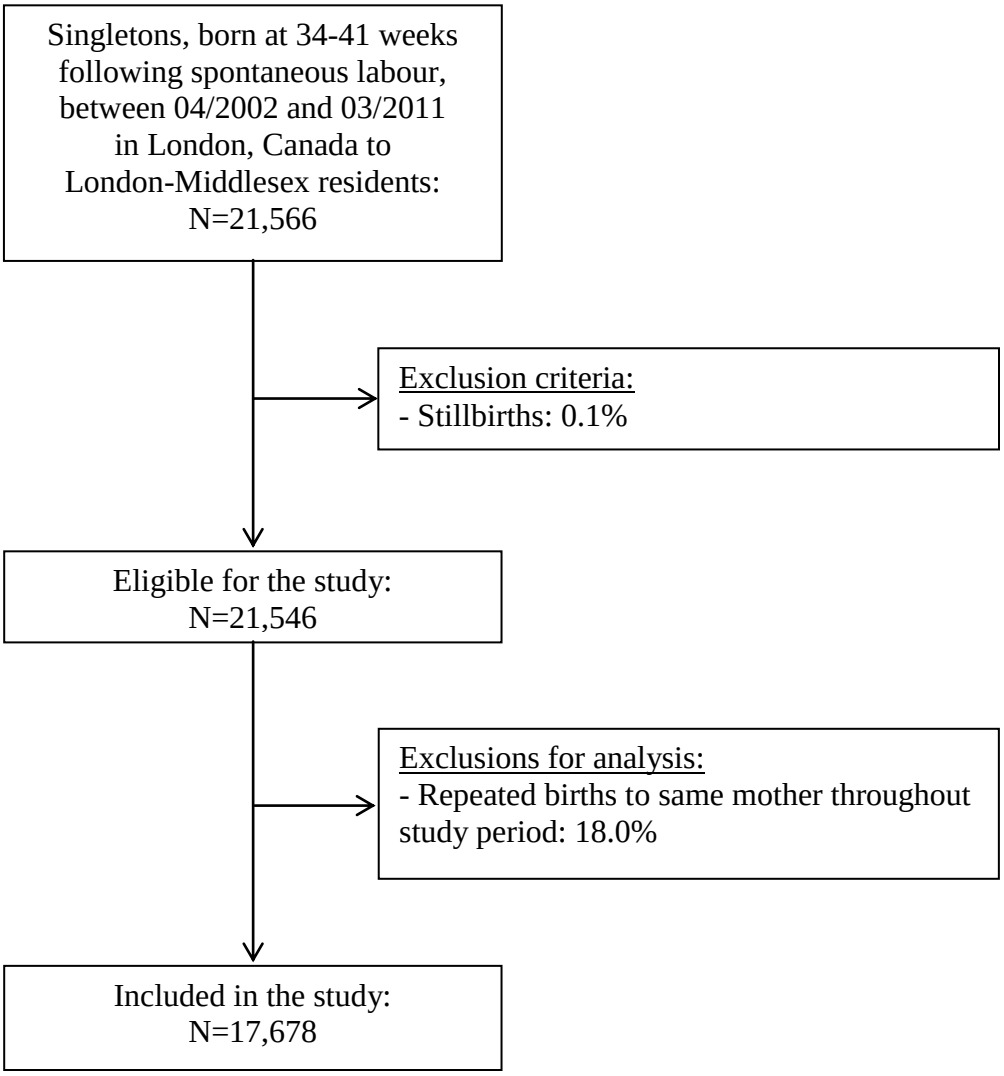

Table 5.1. Sample Characteristics (N=17,678).

	N	%
Prenatal socio-demographic and lifestyle variables		
Maternal age		
<20 years	988/17,214	5.8
20-34 years	13,329/17,214	77.4
≥35 years	2,897/17,214	16.8
Maternal marital status		
Single (never married)	2,817/17,331	16.3
Widowed, separated, divorced	202/17,331	1.1
Common-law	2,772/17,331	16.0
Married	11,522/17,331	66.6
Median neighbourhood family income (CAD)		
$50,000-$59,999	4,179/17,678	23.5
$60,000-$69,999	6,862/17,678	38.8
$70,000-$79,999	2,810/17,678	15.9
$80,000-$89,999	2,640/17,678	14.9
$90,000 or more	1,187/17,678	6.7
Parity		
Nulliparous	7,873/17,678	44.5
Primi/multiparous	9,805/17,678	55.5
Previous preterm delivery		
Yes	976/17,678	5.5
No	16,702/17,678	94.5
Previous abortion (spontaneous, induced)		
Yes	5,485/17,677	31.0
No	12,192/17,677	69.0
Prenatal care		
None / inadequate (<4 visits at 36 weeks)	302/17,678	1.7
Normal / adequate	17,376/17,678	98.3
Smoking during pregnancy		
Yes	2,978/17,678	16.9
No	14,700/17,678	83.1
Drug use during pregnancy		
Yes	430/16,923	2.5
No	16,493/16,923	97.5
Alcohol during pregnancy		
Yes	309/17,677	1.8
No	17,368/17,677	98.2
Biological determinants of preterm birth		
Infection and inflammation		
Yes	1,120/17,678	6.3
No	16,558/17,678	93.7

	N	%
Placental ischemia and other hypoxia		
Yes	2,832/17,678	16.0
No	14,846/17,678	84.0
Other biological determinants		
Yes	697/17,678	3.9
No	16,981/17,678	96.1
Other pre-delivery covariates		
Other maternal medical conditions		
Yes	3,383/17,678	19.1
No	14,295/17,678	80.9
Congenital anomalies (minor and major)		
Yes	776/17,678	4.4
No	16,902/17,678	95.6
Fetal sex		
Male	9,026/17,661	51.1
Female	8,635/17,661	48.9

Table 5.2. Unadjusted and Adjusted Associations between Covariates and Late Preterm and Early Term Birth.

	% LPT	% ET	Unadjusted OR (95% CI)		Adjusted OR (95% CI)	
			Late preterm	Early term	Late preterm	Early term
Prenatal socio-demographic and lifestyle variables						
Maternal age						
<20 years	5.9	22.7	1.08 (0.81, 1.43)	1.01 (0.86, 1.18)	1.27 (1.04, 1.54)	0.97 (0.87, 1.07)
20-34 years	5.1	22.6	reference	reference	reference	reference
≥35 years	5.5	22.7	1.17 (0.98, 1.39)	1.02 (0.92, 1.12)	0.75 (0.54, 1.04)	1.08 (0.90, 1.29)
Maternal marital status						
Single (never married)	7.1	22.3	1.58 (1.33, 1.87)	1.01 (0.91, 1.11)	1.30 (1.05, 1.61)	0.98 (0.87, 1.11)
Widowed, separated, divorced	4.5	27.2	1.02 (0.52, 2.01)	1.27 (0.93, 1.75)	0.92 (0.45, 1.87)	1.25 (0.90, 1.74)
Common-law	6.0	21.5	1.28 (1.06, 1.53)	0.95 (0.86, 1.05)	1.12 (0.91, 1.37)	0.93 (0.83, 1.03)
Married	4.6	22.7	reference	reference	reference	reference
Median neighbourhood income						
$50,000-$59,999	5.9	23.0	1.51 (1.10, 2.07)	1.06 (0.90, 1.23)	1.35 (0.95, 1.93)	1.06 (0.90, 1.25)
$60,000-$69,999	5.7	22.8	1.46 (1.07, 1.98)	1.04 (0.89, 1.21)	1.45 (1.03, 2.04)	1.07 (0.91, 1.25)
$70,000-$79,999	4.6	21.8	1.14 (0.81, 1.61)	0.97 (0.82, 1.14)	1.10 (0.75, 1.59)	1.00 (0.84, 1.19)
$80,000-$89,999	4.5	22.4	1.11 (0.79, 1.57)	1.00 (0.85, 1.18)	1.15 (0.79, 1.67)	1.03 (0.86, 1.61)
$90,000 or more	4.0	22.5	reference	reference	reference	reference
Parity						
Nulliparous	6.0	20.7	1.22 (1.07, 1.40)	0.83 (0.77, 0.89)	1.82 (1.54, 2.16)	0.91 (0.84, 1.93)
Primi/multiparous	4.7	24.2	reference	reference	reference	reference
Previous preterm delivery						
Yes	18.6	35.4	6.55 (5.43, 7.90)	2.58 (2.23, 2.99)	8.46 (6.75, 10.61)	2.43 (2.08, 2.84)
No	4.5	21.9	reference	reference	reference	reference
Previous abortion						
Yes	5.6	23.0	1.11 (0.96, 1.27)	1.04 (0.96, 1.12)	---	---
No	5.2	22.4	reference	reference		

	% LPT	% ET	Unadjusted OR (95% CI)		Adjusted OR (95% CI)	
			Late preterm	Early term	Late preterm	Early term
Prenatal care						
None / inadequate	15.6	27.5	3.87 (2.78, 5.37)	1.55 (1.19, 2.02)	2.77 (1.81 4.23)	1.47 (1.09, 1.98)
Normal / adequate	5.1	22.5	reference	reference	reference	reference
Smoking during pregnancy						
Yes	7.2	23.7	1.53 (1.30, 1.79)	1.11 (1.01, 1.22)	---	---
No	4.9	22.4	reference	reference		
Drug use during pregnancy						
Yes	12.3	27.4	2.94 (2.17, 3.99)	1.46 (1.17, 1.82)	1.77 (1.22, 2.55)	1.22 (0.95, 1.57)
No	5.0	22.6	reference	reference	reference	reference
Alcohol during pregnancy						
Yes	7.8	26.2	1.62 (1.05, 2.48)	1.27 (0.98, 1.65)	---	---
No	5.3	22.5	reference	reference		
Biological determinants of preterm birth						
Infection and inflammation						
Yes	11.0	19.7	2.34 (1.91, 2.86)	0.90 (0.77, 1.05)	2.07 (1.65, 2.60)	0.88 (0.75, 1.04)
No	4.9	22.8	reference	reference	reference	reference
Placental ischemia and other hypoxia						
Yes	9.6	25.7	2.43 (2.09, 2.82)	1.33 (1.21, 1.46)	2.21 (1.88, 2.61)	1.25 (1.13, 1.39)
No	4.5	22.0	reference	reference	reference	reference
Other biological determinants						
Yes	13.6	38.2	4.17 (3.29, 5.29)	2.63 (2.23, 3.11)	3.61 (2.77, 4.69)	2.52 (2.12, 3.00)
No	5.0	22.0	reference	reference	reference	reference
Other pre-delivery covariates						
Other medical conditions						
Yes	6.9	24.0	1.47 (1.26, 1.71)	1.13 (1.04, 1.24)	1.30 (1.09, 1.18)	1.08 (0.98, 1.18)
No	4.9	22.3	reference	reference	reference	reference

	% LPT	% ET	Unadjusted OR (95% CI)		Adjusted OR (95% CI)	
			Late preterm	Early term	Late preterm	Early term
Congenital anomalies						
Yes	7.2	25.6	1.50 (1.13, 1.99)	1.23 (1.04, 1.45)	1.35 (0.99, 1.84)	1.30 (1.09, 1.54)
No	5.2	22.1	reference	reference	reference	reference
Fetal sex						
Male	6.0	23.1	1.38 (1.21, 1.59)	1.08 (1.00, 1.16)	1.35 (1.16, 1.56)	1.05 (0.97, 1.13)
Female	4.5	22.1	reference	reference	reference	reference

--- : p>.20 in final model.

Chapter 6

Discussion

This chapter summarizes the results of this thesis and their implications. The strengths and limitations of the thesis are discussed, and future research directions are described.

Current evidence, reviewed in Chapter 2, suggests that late preterm and early term birth are associated with poor neonatal and developmental outcomes. However, most previous studies have not fully addressed the roles of factors leading to or associated with early birth that could also influence outcomes. It remains unclear to what extent poor outcomes among individuals born late preterm and early term are associated with physiological immaturity per se or with related biological and social factors.

The overall aim of this thesis was to elucidate the role that gestational age plays in determining the risk of poor neonatal and developmental outcomes among individuals born late preterm and early term by examining the contribution of gestational age to these outcomes in the context of biological determinants of preterm birth and proximal social processes.

6.1 Brief Summary of Results

6.1.1 The Samples

The samples for this thesis came from two data sources: a perinatal database and Discharge Abstract Database (for the *first objective* and *third objective*) and the National Longitudinal Survey of Children and Youth (**NLSCY**) (for the *second objective*).

In the full perinatal database sample (described in Chapter 3), 4.7% of infants were born late preterm, 24.8% were born early term, and 70.5% were born full term. The majority of their mothers were between 20 and 34 years of age (78.2%), married or common-law (83.9%), and living in neighbourhoods with a median family income of $60,000 per year or greater (76.9%). There were few women with unhealthy behaviours during pregnancy: 16.7% smoked, 2.5% used drugs, and 1.6% used alcohol. Although measures of family-

level income and maternal education were not collected, the available characteristics suggest a sample with a relatively high socioeconomic status. (The subsample of women with spontaneous births described in Chapter 5 had similar characteristics.)

In the NLSCY sample (Chapter 4), 7.2% of children were born late preterm, 28.7% were born early term, and 64.0% were born full term. The majority of their mothers were 20 years or older at their birth (96.2%), consistently lived in two parent families (85.1%), had some post-secondary education or higher (69.4%), and had consistently adequate family income (81.7%). Few women reported unhealthy behaviours during pregnancy: 18.2% reported smoking, and 15.6% reported any alcohol use. The sample at 2 to 3 years of age represented 81.5% of the original sample (at 0 to 1 years), and the sample at 4 to 5 years of age represented 66.4% of that original sample. Compared to their baseline characteristics, respondents at the time their children were aged 2 to 3 and 4 to 5 years were more likely than non-respondents to be 20 years or older at the child's birth, to consistently live in two-parent families, to have some post-secondary education or higher, and to have consistently adequate family income. (Other characteristics indicative of higher socioeconomic status, such as healthy lifestyle during pregnancy and positive family functioning, were also more common.) The sample available to the analyses therefore had a slightly higher socioeconomic status on average than the original sample.

The proportions of individuals born late preterm and early term were higher in the NLSCY sample compared to the perinatal database sample. This could be due to the nature of the study populations that are represented. The perinatal database covered a specific geographic area (i.e., City of London and Middlesex County) with a fairly uniform socioeconomic status, while the NLSCY sample covered urban and rural areas across all 10 provinces, and special effort was made to represent families living at the lower end of the socioeconomic spectrum (1). However, because different measures were used to capture socioeconomic status in the two samples, it is difficult to make direct comparisons to verify this assumption. It is possible that differences in the gestational age distribution could be due to measurement (i.e., late preterm and early term birth may have been over-reported in the NLSCY due to imperfect maternal recall). Nonetheless, similar to published statistics (2), the median gestational age in both samples was 39 weeks.

Moreover, despite the described variation between samples, proportions of late preterm and early term birth were, overall, in line with previous Canadian findings (3).

6.1.2 Neonatal Outcomes of Late Preterm and Early Term Birth

Neonatal intensive care unit (**NICU**) triage/admission was measured in the perinatal database, and diagnoses consistent with neonatal respiratory morbidity were obtained from International Classification of Disease (**ICD**) codes in the Discharge Abstract Database. The overall rate of NICU triage/admission was 6.9% (38.9% in late preterm, 7.7% in early term, and 4.6% in full term infants). The overall rate of neonatal respiratory morbidity was 3.5% (17.7% in late preterm, 3.8% in early term, and 2.5% in full term infants). After controlling for confounders, infants born late preterm and early term were more likely to experience NICU triage/admission and neonatal respiratory morbidity compared to those born full term. However, gestational age was a partial mediator between infection and inflammation, placental ischemia and other hypoxia, and other biological determinants and both NICU triage/admission and neonatal respiratory morbidity. Moreover, there was evidence of moderation by the biological determinants of preterm birth such that infants exposed to both early birth and placental ischemia and other hypoxia or other biological determinants had excess risk for poor neonatal outcomes.

The results of the main effects analyses are consistent with literature showing that infants born late preterm and early term are at increased risk for NICU admission (4-6) and longer hospital stay (6-8) as well as respiratory (4, 6, 7, 9, 10) and other (4-7, 9-12) neonatal diagnoses. The results of the mediation analysis are consistent with theory suggesting that gestational age (or birth weight) exists on the etiological pathway to poor neonatal outcomes (13, 14). To our knowledge, only one study has examined the moderating role of maternal medical conditions on the relationship between late preterm birth and neonatal morbidity (15); the current findings are consistent with this study and build on it by grouping maternal medical conditions according to pathways with a common pathophysiological mechanism. Overall, these results suggest that, although gestational age remains a strong predictor of poor neonatal outcomes even during the late

preterm and early term periods, biological determinants of preterm birth may act through and with gestational age to produce these poor neonatal outcomes.

6.1.3 Developmental Outcomes of Late Preterm and Early Term Birth

In the NLSCY, developmental delay at 2 to 3 years of age was measured by maternal self-report using the Motor and Social Development Scale (1), and receptive vocabulary delay was measured by direct interviewer assessment using the Peabody Picture Vocabulary Test-Revised (16). The overall rate of developmental delay in 2 to 3 year olds was 14.2% (16.7% in late preterm, 14.3% in early term, and 13.9% in full term). The overall rate of receptive vocabulary delay in 4 to 5 year olds was 13.0% (13.0% in late preterm, 13.9% in early term, and 12.7% in full term). In the unadjusted analyses, children born late preterm were more likely than those born full term to have developmental delay at 2 to 3 years of age. However, after controlling for confounders, there was no evidence of increased risk for developmental delay or for receptive vocabulary delay among children born late preterm or early term. We hypothesized that there could be significant risks associated with late preterm and early term birth among families with important proximal social risks (i.e., poor parenting). Although interactions between gestational age and parenting were not statistically significant, the main effects for parenting showed a strong association with both developmental delay and receptive vocabulary delay, even after controlling for important aspects of the social context including family structure and family resources, which were also strong predictors of both outcomes.

Although our finding of no effect of late preterm and early term birth on developmental outcomes (in adjusted analyses) contrasts with many previous studies, several others also found no association (17-19). The main effects for parenting are consistent with literature showing the importance of proximal social processes even after controlling for social context (20, 21). It is important to note that, consistent with previous research (4, 5) and the Chapter 3 results, we found a strong association between late preterm birth and neonatal special care in the NLSCY sample. Because this study is one of the first to adequately control for the social environment, it is possible that these findings show that,

among births closer to full term, the impact of mild prematurity loses strength after the neonatal period and that social factors, particularly proximal social processes, become more important predictors of child development.

6.1.4 Biological Determinants of Late Preterm and Early Term Birth

Biological determinants of preterm birth (i.e., infection and inflammation, placental ischemia and other hypoxia, and other biological determinants) were measured according to diagnoses recorded in the perinatal database. Among births following spontaneous labour, 6.3% were exposed to infection and inflammation, 16.0% to placental ischemia and other hypoxia, and 3.9% to other biological determinants (i.e., pre-existing or gestational diabetes mellitus, polyhydramnios, or oligohydramnios). After controlling for confounders, infants exposed to infection and inflammation were more likely than those not exposed to be born late preterm (but not early term). Infants exposed to placental ischemia and other hypoxia as well as other biological determinants were more likely than those not exposed to be born both late preterm and early term.

These findings build on a body of literature which suggests that spontaneous preterm birth is caused by multiple pathological mechanisms that trigger the final common pathway to parturition (22). While a great deal of literature has focused on understanding this "preterm parturition syndrome" (22-25), most previous studies have focused on very preterm birth or preterm birth in general (26-28). This analysis showed that pathological triggers of spontaneous preterm labour are associated with even late preterm and early term birth. Due to the focus of previous literature on the causes of very preterm birth, most research has examined biological determinants of infectious origin, which are more commonly associated with birth at earlier gestational ages (22-23). The current analysis highlights biological determinants of preterm birth which are more relevant to birth closer to full term (e.g., placental ischemia and other hypoxia and other biological determinants, [diabetes mellitus/hydramnios]). These pathological triggers have implications for fetal and neonatal health and are also associated with medically indicated birth (29, 30), thus adding strength to the finding of gestational age as a partial mediator between biological determinants of preterm birth and poor neonatal outcomes.

6.2 Implications

6.2.1 Assessment of Neonatal Risk in Infants Born Late Preterm and Early Term

The finding of increased risk for neonatal morbidity associated with late preterm and early term birth has implications for clinical practice at delivery, during the birth hospitalization, and at hospital discharge. The results of this thesis show that it should not be assumed that infants born late preterm and early term are functionally similar at birth compared to those born full term (31). This means that healthcare professionals should be prepared to provide special care that would have traditionally been assumed necessary only for infants born earlier (e.g., at less than 34 weeks gestation). Because infants born prior to full term are at increased risk for respiratory depression and distress at birth (32), the delivery team should be aware of the estimated gestational age and should be ready to perform resuscitation or to administer surfactant or oxygen when necessary (33). During the birth hospitalization, although it is preferred to keep the mother and newborn together, it may be necessary to admit the newborn to a special care nursery when there is a need for cardio-respiratory monitoring, incubator use, or intervention (33). In recent years, there has been a trend toward early discharge (less than 2 days) of infants born at term (i.e., 37 weeks or later) and, sometimes, late preterm (34, 35). However, infants born late preterm (36) and even early term (8) are at increased risk for hospital readmission following the delivery discharge, with jaundice and infection being among the most common reasons for readmission (36). Physicians should therefore exercise caution in determining whether an infant born prior to full term can be discharged early, and respiratory function (as well as serum bilirubin levels, feeding ability, and ability to maintain thermal homeostasis) should be carefully considered (33).

In his article on neonatal management of infants born late preterm, Whyte (33) suggests that “routine” assessments of all infants born late preterm or early term may be unwarranted since they are likely to generate a high rate of false-positive results which would result in unnecessary testing and separation from the mother. He instead suggests that risk assessment, based on maternal history, birth events, and physical examination of the newborn, should be used to determine the need for further follow-up and/or admission

to special care. For example, although it is unlikely that all late preterm and early term newborns should undergo blood cultures or receive prophylactic antibiotics for sepsis, a maternal history of infection and inflammation may better define their risk and justify further testing or intervention in such newborns (33). The finding that biological determinants of preterm birth may act through and with gestational age to produce poor outcomes provides evidence of high risk groups among infants born late preterm and early term which may benefit from closer monitoring during the newborn period.

6.2.2 Follow-up of Late Preterm and Early Term Births in Childhood

In their 2009 article on early intervention eligibility criteria, Marks et al. (37) recommended lowering developmental screening thresholds to include children born late preterm. While this thesis found increased risk for developmental delay associated with late preterm birth in unadjusted analyses, the association was not statistically significant after controlling for confounders. Parenting, a proximal social process, proved to be a more important predictor of poor developmental outcomes, even after controlling for other aspects of the social environment, including family resources. It is possible that among births close to full term, biological risk factors become less important, and social factors become more important with increasing age (38-41). If this is the case, rather than targeting screening mainly on the basis of biological risk (i.e., gestational age at birth), social factors such as parenting behaviours may be more appropriate criteria among children with only mild biological risks. While a child's health status at birth is not modifiable, parenting behaviours are (42). Research shows that interventions on parenting have the greatest impact on child development when administered early (i.e., infancy vs. toddler-preschool) (43). Given the null findings associated with late preterm and early term birth found in this thesis and several other studies, it may be advisable to focus greater effort on these social factors for populations born closer to full term.

6.2.3 Prevention of Early Birth Prior to Full Term

The finding of multiple pathological mechanisms associated with spontaneous late preterm and early term birth has implications for the prevention of early birth. The heterogeneous etiology of birth prior to full term (even at later gestational ages) suggests

the need for targeted interventions aimed at specific clinical conditions rather than early birth as a whole (44). For example, while the use of antimicrobial or anti-inflammatory treatments for preterm labour may prevent preterm birth among women with infection and inflammation, women with placental ischemia and other hypoxia would require different interventions (45). The heterogeneous etiology of "pre-term" birth (even at late preterm and early term gestations) therefore presents a significant challenge to interventions aimed at prolonging gestation to full term.

It should be noted that although incomplete fetal maturation prior to 39 weeks gestation (46) suggests the need to prevent late preterm and early term birth, the risks of prolonging pregnancy should also be carefully considered. Early birth may have survival value in terms of protecting the fetus from a "hostile intrauterine environment" (47, 48). The recent increase in medically indicated preterm birth has been accompanied by a decline in perinatal mortality (49) and stillbirth (50, 51). The biological determinants of preterm birth each contribute to a pathological intrauterine environment (52, 53) and, in addition to their association with spontaneous late preterm and early term birth shown in this thesis, are also cause for intervention when there is concern for maternal or fetal well-being (54, 55). The prevention of early birth may not always be advised. It is impossible to predict with certainty what would have happened to infants who were born early had they remained in utero. Therefore, the decision to deliver early or not, although informed by the evidence generated from this thesis, will need to be made at the individual level, weighing up the risks and benefits of expectant management.

6.3 Study Strengths

This thesis has several strengths that allowed it to improve on the limitations of previous studies. First, the conceptual models presented in the thesis are novel in this research field. To our knowledge, previous studies examining neonatal outcomes of late preterm and early term birth have not used a conceptual model to guide analyses. This has resulted in a variety of methods used to treat the biological determinants of preterm birth (e.g., ignore, exclude, control for). More detailed causal thinking surrounding the relationship between biological determinants of preterm birth and gestational age as well

as the pathological implications of these biological determinants of preterm birth allowed for the use of a more complex statistical model to better isolate the effect of gestational age on neonatal outcomes. Similarly, most studies examining developmental outcomes of late preterm and early term birth have relied on a biomedical model of disease, which tends to ignore social influences on development (56-58). By using a hybrid of Bronfenbrenner's bioecological model (59) and Escalona's concept of double jeopardy (60), it was possible to thoroughly account for and explain the roles of social factors when trying to answer a predominantly biological question that is nonetheless situated in a social context. The use of conceptual models in this thesis therefore allowed for more refined causal thinking than was used in previous studies.

Second, both data sources had extensive information on covariates which allowed for better elucidation of the role of gestational age in determining the risk of poor neonatal and developmental outcomes. In the perinatal database, detailed information on maternal pre-pregnancy and pregnancy-related health was available; it was therefore possible to fulfill the detailed conceptualization of the biological determinants of preterm birth. Moreover, detailed information on prenatal socio-demographic and lifestyle variables, other maternal medical conditions, and labour variables allowed these factors to be controlled for in the analyses. The NLSCY includes a wide range of questions related to the social environment; this allowed for an examination of several dimensions of parenting, including parenting interactions, parenting effectiveness, and parenting consistency. Furthermore, it was possible to control for a wide range of covariates, including perinatal variables, family structure, family resources, and family functioning. This is a significant improvement on previous research, which incompletely accounted for factors leading to or associated with early birth and other covariates.

Third, the large sample sizes available in both the perinatal database and the NLSCY allowed for tests of interaction. It is generally recommended that the required sample size be multiplied by four when conducting interaction analyses (61); studies therefore require a large sample size to test such relationships with sufficient power. The samples available in both data sources made it possible to quantitatively test complex relationships shown in the conceptual models.

Fourth, both data sources captured samples which were broadly generalizable to the population. The perinatal database captures information on all hospital births in London, Ontario. In Ontario, over 98% of all births, including those attended by a midwife or nurse practitioner, take place in a hospital (62); therefore, hospital births captured the vast majority of births in the region. Moreover, in contrast with many of the previous neonatal studies, which were restricted to single tertiary care centres, we utilized data from both a level II and level III centre, making results more applicable to the obstetrical population as a whole. For the developmental study, the NLSCY captures information on all children in Canada (except those living in institutions or on reserves or whose parents are members of the Armed Forces) (1). Special effort was made to recruit participants representative of all Canadian provinces, both geographically and according to socioeconomic status (1). It is therefore expected that results of the developmental analyses will be generalizable to the Canadian population.

6.4 Study Limitations

Several limitations should be considered when interpreting the findings from this thesis. First, measurement of gestational age in both data sources was imperfect. The perinatal database recorded gestational age from charts, presumably measured according to mother's last menstrual period or, if different from a first trimester ultrasound by more than 4 days, ultrasound estimate. Ultrasound estimates, which rely on measurements of fetal crown-rump length (first trimester) and biparietal diameter or head circumference (second trimester), are based on the assumption that fetal size early in gestation varies according to gestational age alone (63, 64). However, as gestation progresses, variability in fetal size may be explained by factors such as fetal growth restriction as opposed to gestational age per se (64). Although using last menstrual period and ultrasound estimates together reduce the incidence of errors (63), it remains possible that there was misclassification of gestational age, particularly between adjacent categories such as late preterm/early term and early term/full term. Likewise, measurement of gestational age in the NLSCY was limited by use of maternal self-report. There is disagreement among studies regarding the accuracy of maternally recalled gestational age. For example, Adegboye et al. (65) reported that only 42% of maternally recalled gestational ages were

identical to medical records; 94% were within 2 weeks, and there was a slight tendency to overestimate gestational age. In contrast, Hakim et al. (66) reported that 74% of mothers reported gestational age within 1 week of medical record estimates, and Sou et al. (67) reported differences between estimates of only 0.5 weeks, on average. As with the perinatal database, it is therefore possible that there was some misclassification of gestational age in the NLSCY. However, it should be noted that responses in relation to due date (i.e., days or weeks early or late, as in the NLSCY) appear to be more accurate than those in relation to length of gestation, and responses are more accurate the closer questioning is to birth (i.e., at 0 to 1 years, as in the NLSCY vs. later in childhood) (68).

Second, a related issue is whether gestational age, even if measured accurately, is a valid marker of fetal functional maturity. To date, gestational age is the best available marker for functional maturity at birth. However, as described by Iams (69), further information is needed on what makes a fetus mature so that measurements are more robust. Improvements to the conceptualization and measurement of fetal maturity would help to more accurately answer questions such as those posed in this thesis and to better establish milestones such as the definition of "full term" birth.

Third, there may also have been misclassification of the outcome variables in Chapter 3 and Chapter 4. NICU triage/admission does not reflect morbidity that does not result in triage or admission; for example, hyperbilirubinemia may be treated with phototherapy in the well-baby nursery. Moreover, NICU admission may reflect bed availability and other administrative decisions (70, 71) as well as clinical precautions (e.g., observation) (44) rather than morbidity per se. Therefore, depending on the circumstances surrounding the infant's birth and the availability of resources at the time of birth, NICU triage/admission may have under- or overestimated neonatal morbidity. It is also possible that neonatal respiratory morbidity was under-reported. In a previous study examining the validity of diagnostic codes in the Discharge Abstract Database, Joseph et al. (72) found that respiratory distress syndrome, as reported in the Discharge Abstract Database, had a sensitivity of 50.9% when compared with information from the Nova Scotia Atlee Perinatal Database (specificity = 99.8%). The authors found that when they added procedural codes for intubation to create a "severe respiratory distress" variable,

agreement between the datasets was nearly 100% (sensitivity = 100.0%, specificity = 99.6%). Although a similar approach could have been used in the current study, this would have resulted in restricting respiratory morbidity to severe respiratory morbidity, which would have made the outcome rarer and therefore of less clinical relevance to this "almost full term" population. (It should be noted that when Joseph et al. compared "any respiratory distress" in the Discharge Abstract Database and the Nova Scotia Atlee Perinatal Database, sensitivity was 94.2% and specificity was 96.6%. This conceptualization of respiratory morbidity is probably more similar to the one used in the current study.) It is possible that maternal report of developmental delay was also biased. Previous studies have noted that maternal report of child outcomes may be distorted by maternal mental health or socioeconomic status (73-75). However, a seminal review article failed to find an association between maternal depression and misrepresentation of developmental outcomes (76). Moreover, several studies have found maternal report of developmental outcomes to be highly accurate (77, 78), and parental concerns are a valuable component of clinical assessments of child development since children may under-perform in an unfamiliar clinician's office (77).

Fourth, this thesis was limited by unavailability of some variables required to complete the neonatal and developmental conceptual models (Figure 2.2 and Figure 2.3). In Chapter 3 and Chapter 5, it was not possible to measure endocrine triggers since maternal depression and anxiety were noted in the perinatal database on the basis of medication use and not diagnosis (79). Similarly, for Chapter 4, the NLSCY only had limited information on biological determinants of preterm birth (i.e., hypertension during pregnancy, size for gestational age, and diabetes mellitus during pregnancy). Moreover, although delivery mode was available in the NLSCY, the nature of labour onset (i.e., spontaneous or medically indicated) was not measured. Inability to control for all desired variables is a limitation of many studies using secondary data. Prospective collection of data designed to specifically answer the study questions would have been preferable (69); however, due to the large sample sizes needed to address the thesis objectives and the length of follow-up needed for Chapter 4, this was not feasible. Despite this limitation, however, this thesis controlled for a wider and more detailed set of confounders than that considered by previous studies in this area of research.

6.5 Future Directions

This work would benefit from testing the conceptual model for the *first objective* and the *third objective* using a data source which has more detailed information on biological determinants of preterm birth. First, this data source should contain diagnostic information on endocrine triggers. There is evidence that maternal depression and anxiety are related to both early birth and poor neonatal health (80). Thus, we would expect that endocrine triggers would also act through and with gestational age to produce neonatal morbidity among infants born late preterm and early term. Incorporating endocrine triggers into statistical models would therefore further explain the causes of spontaneous late preterm and early term birth as well as the association between early birth and poor neonatal outcomes in the context of the biological determinants of preterm birth. Second, this research would benefit from further detail on the timing, severity, and management of all biological determinants of preterm birth. Such information could provide further clues regarding the causal mechanisms underlying these processes.

Future research could add to the *first objective* by applying different outcomes of importance to late preterm and early term birth to the conceptual model. Previous studies have suggested that infants born late preterm and early term are also at increased risk for sepsis and hypoglycemia (4, 6, 7, 10, 22). Because these neonatal diagnoses are more specific in etiology than NICU triage/admission and neonatal respiratory morbidity, it is expected that they would show stronger associations with certain biological determinants of preterm birth (e.g., sepsis with infection and inflammation; hypoglycemia with pre-existing and gestational diabetes mellitus). By inserting these outcomes into the conceptual model, it could be determined whether particular biological determinants of preterm birth act through and with gestational age to produce particular neonatal conditions. Such a finding would add strength and specificity to Whyte's (33) suggestion that surveillance of infants born late preterm (or early term) should be based on specific risk factors for poor outcomes, including maternal history.

Before a strong recommendation regarding routine developmental follow-up of late preterm and early term birth is considered, evidence needs to be built on studies with

detailed and accurate measures of both biological and social risk factors. While this thesis makes a significant improvement on previous research by thoroughly accounting for the role of the social environment (both proximal social processes and social context variables), there is still a degree of uncertainty about the results due to the use of maternal report of gestational age. Future research should add to the *second objective* by applying the conceptual model to a data source with both adequate representation of social factors and prospectively collected measurement of gestational age (63). Although it is acknowledged that "gold standard measurement" of all desired variables is a difficult and resource-intensive undertaking, such efforts would reduce the dichotomy between "biological research" and "social research" in this area and would significantly improve understanding of the developmental outcomes of late preterm and early term birth.

6.6 Conclusions

Late preterm and early term birth represent a clinically significant proportion of live births. Since 1995, the incidence of preterm birth has risen by 17% (2), and as of 2004, preterm birth accounted for 8.2% of all births in Canada (81). Late preterm infants now represent nearly 75% of preterm births (i.e., approximately 6% of all births) (2). Moreover, early term infants now account for approximately 17.5% of all births (81, 82). Even a small increase in risk in these groups can therefore have a large population impact. A greater understanding of the determinants of poor outcomes in individuals born late preterm and early term is therefore critical.

This thesis makes a significant contribution to the literature by demonstrating that poor neonatal outcomes among infants born late preterm and early term are not only due to physiological immaturity but also to biological determinants of preterm birth acting through and with gestational age to produce poor outcomes. Beyond the neonatal period, among births at these later gestational ages, social factors may be the most important influences on development. The findings of this thesis contribute to an understanding of the role of gestational age in determining the risk of poor neonatal and developmental outcomes in individuals born late preterm and early term, in the context of biological and social factors leading to or associated with early delivery.

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APPENDICES

Appendix A

Objective One and Objective Three Details

A.1 Data Source Details

A.1.1 Perinatal Database

Managed by the London Health Sciences Centre Department of Obstetrics and Gynaecology, the perinatal database contains information on all births ≥20 weeks or ≥500 grams which occurred at St. Joseph's Health Care or London Health Sciences Centre-Victoria Hospital in London, Ontario. Following delivery, data for each birth are abstracted from the medical chart and are entered into the perinatal database by database personnel. Most of the information is obtained from the mother's antenatal medical record (which is completed prospectively throughout the pregnancy), the obstetrical risk summary form, and the infant's birth summary (which is completed at delivery). At the time of the thesis data collection, the current version of the perinatal database contained data on births from 1995 to June 2011 for St. Joseph's Health Care and for births from 1998 to March 2012 for London Health Sciences Centre-Victoria Hospital.

The perinatal database was constructed in 1981 using Vital Statistics Act guidelines. Data are stored in Microsoft Access, and the database entry system has built-in data quality checks. These checks look for improbable values or combinations of values. Logic checks of relevance to this thesis include: (a) primiparous with a previous caesarean section; (b) mismatched forceps and delivery type; (c) inappropriate birth weight for gestational age; (d) maternal age less than 15 or greater than 45 years; and (e) mismatched labour or delivery type and indications for caesarean section or induction. There are also flags for missing birth weight, gestational age, parity, labour type, forceps, vacuum extraction, infant chart number, postal code, and neonatal intensive care unit (**NICU**) triage/admission. Each month, the number of births in the perinatal database is balanced against birthing unit and NICU log books.

The perinatal database has ethics approval from the University of Western Ontario Health Sciences Research Ethics Board, which allows it to obtain and store data for all deliveries, without patient consent, for the purposes of clinical evaluation and research. It is therefore complete for virtually every hospital birth occurring in London.

A.1.2 Discharge Abstract Database

At the national level, the Discharge Abstract Database is managed by the Canadian Institute for Health Information (**CIHI**). It was developed in 1963 and contains information on all "separations" from acute care hospitals in all Canadian provinces and territories except Quebec. These "separations" include discharge, death, sign-out, or transfer to another facility. The Discharge Abstract Database contains administrative, socio-demographic, and clinical information for all such separations, including obstetrical deliveries (for both mother and infant) (1).

At London Health Sciences Centre, discharge abstracts are created by Health Records personnel who use the CIHI Discharge Abstract Database Abstracting Manual to convert information from the medical chart to diagnostic or procedural codes using the International Classification of Disease (**ICD**) coding system. Abstractors use specialized software approved by CIHI which incorporates data quality control measures, including cross-data logic checks and flags for missing information (1). Data must go through these quality checks prior to being submitted to CIHI (1). For the current study, validated data from the Discharge Abstract Database were obtained directly from London Health Sciences Centre Health Records (for all births which occurred at St. Joseph's Health Care and London Health Sciences Centre-Victoria Hospital during the study period).

International Classification of Disease

All diagnoses in the Discharge Abstract Database are coded using the ICD system. The ICD is a standardized medical classification system which is developed and maintained by the World Health Organization (**WHO**) to monitor and assess the health of populations. Since 1900, the ICD has been revised every 10 years to maintain use of the current understanding of disease etiology and terminology. The most current version is the ICD-10, which was approved in 1990 and put to use worldwide in 1994. The WHO allowed CIHI to modify the ICD-10 to make it applicable to the Canadian healthcare system. CIHI thus developed the ICD-10-CA, which was implemented in Ontario in 2002. The ICD-10-CA section of particular interest to this study is Chapter XVI ("Certain conditions originating in the perinatal period"), which covers codes P00 to P99.

A.1.3 Linkage of Datasets for Chapter 3

The perinatal database and the Discharge Abstract Database were linked to obtain more detailed neonatal outcomes for the Chapter 3 analyses. An exact match was performed by the author using the following steps.

First, after derivation of the study sample eligible for Chapter 3 (N=39,438), a first attempt at linkage was performed using SAS MERGE, with infant chart number in the BY statement. A small number of records (N=332, 0.8%) had an infant chart number in the perinatal database that did not match an infant chart number in the Discharge Abstract Database. For these records, variables available in both datasets (i.e., maternal chart number, infant sex, infant date of birth, and gestational age) were printed for each dataset, and infant chart number in the perinatal database was manually "corrected" for all records with exactly matching corresponding information in the Discharge Abstract Database. (Most of the errors in infant chart number were missing digits in one of the datasets.) Only N=57 (0.1%) of records could not be manually corrected. The linkage was attempted again, excluding these 57 records. All records were linked successfully.

Following this, all linked records were checked on common variables to ensure that matches were correct. As can be seen in Figure 3.1, there were very few records (N=631, 1.6%) with discrepancies on one or more of these common variables. Note that maternal chart number matched for all records. It is therefore likely that discrepancies were due to errors in one of the datasets as opposed to incorrect linkages. For example, since more than one estimate for gestational age may be noted in the medical chart, it is possible that the data abstractor for the perinatal database and the data abstractor for the Discharge Abstract Database chose different values to enter. Since the perinatal database abstractor has more detailed knowledge of perinatal medicine and was trained to verify gestational age using other information in the medical chart, the perinatal database gestational age estimate was chosen to be the "true" value. However, to be conservative, cases with gestational age estimates that diverged by more than one week were excluded. Likewise, cases with discrepant assessments of infant sex and date of birth were also excluded.

A.2 Variable Selection and Measurement

Table A.1 shows evidence for the relationship between each variable and the relevant outcome (for Chapter 3 and Chapter 5) as well as a description of potential measurement issues, where applicable. Table A.2 describes each variable as it was measured in the data source as well as its format for analysis. Table A.3 contains definitions for each of the conditions included in the categories of the biological determinants of preterm birth.

Table A.1. Justification of Inclusion of Variables and Potential Measurement Issues for Chapter 3 and Chapter 5.

Variable	Association with neonatal morbidity (Chapter 3)	Association with early birth (Chapter 5)	Potential measurement issues
Maternal socio-demographic and lifestyle variables			
Maternal age	Infants born to adolescent mothers and mothers ≥35 years are at increased risk for perinatal mortality and NICU admission (2, 3).	Adolescent mothers and mothers ≥35 years are at increased risk for preterm birth (3, 4).	
Maternal marital status	Infants born to unmarried mothers are at increased risk for perinatal mortality (5).	Unmarried mothers are at increased risk for preterm birth (6).	
Maternal income	Low income infants, in Canadian populations, are at increased risk for post-neonatal death (7).	Low income mothers, even in Canadian populations, are at increased risk for preterm birth (7).	Utilization of neighbourhood level income may result in misclassification at the individual level.
Parity	Infants born to nulliparous women are at increased risk for composite measures of neonatal morbidity (8).	Nulliparity is associated with increased risk for preterm birth (9).	
Previous preterm delivery	Previous preterm birth is associated with increased risk for early neonatal mortality (10).	Previous preterm birth is a strong predictor of subsequent early birth (11).	
Previous abortion	Previous abortion is associated with increased risk for perinatal and early neonatal mortality (12).	Previous abortion is a strong predictor of subsequent early birth (11).	

Variable	Association with neonatal morbidity (Chapter 3)	Association with early birth (Chapter 5)	Potential measurement issues
Prenatal care	Although no access to prenatal care is rare in Canada, low or late access are associated with poor neonatal outcomes (13).	Although no access to prenatal care is rare, low or late access, even in Canada, is associated with poor obstetric outcomes (13).	
Smoking during pregnancy	Smoking during pregnancy is associated with NICU admission in the offspring (14).	Smoking during pregnancy is associated with low birth weight and preterm birth (15, 16).	Self-reported smoking during pregnancy underestimates the true prevalence in comparison to cotinine samples (17, 18).
Drug use during pregnancy	Drug use during pregnancy is associated with neonatal morbidity and longer hospital stay in the offspring (19).	Drug use during pregnancy is associated with preterm birth (20).	There is low agreement between self-reported drug use during pregnancy and testing of meconium samples for opioids (21).
Alcohol use during pregnancy	Alcohol use during pregnancy is associated with infant mortality in the offspring (22).	Heavy alcohol use during pregnancy is associated with preterm birth (23).	Women underreport alcohol use, particularly when questions are asked during pregnancy (24).
Biological determinants of preterm birth			
Infection and inflammation	Markers of infection and inflammation are associated with neonatal respiratory morbidity (25, 26).	Markers of infection and inflammation are associated with preterm birth (27).	
Placental ischemia and other hypoxia	Markers of placental ischemia and other hypoxia are associated with NICU admission and neonatal respiratory morbidity (28, 29).	Markers of placental ischemia and other hypoxia are associated with preterm birth (30).	

Variable	Association with neonatal morbidity (Chapter 3)	Association with early birth (Chapter 5)	Potential measurement issues
Other biological determinants	Diabetes (31) and polyhydramnios (32, 33) are associated with poor neonatal outcomes.	Diabetes, polyhydramnios, and oligohydramnios are associated with preterm birth (34, 35).	
Other pre-delivery covariates			
Other maternal medical conditions	There are associations between anemia (36), lupus (37), polycystic ovarian syndrome (38), bowel disease (39) and other conditions (40, 41) and neonatal morbidity.	Chronic maternal medical conditions, (e.g., lupus, polycystic ovarian syndrome, inflammatory bowel disease) are associated with preterm birth (42-44).	
Congenital anomalies	n/a	Congenital anomalies are associated with early birth (32).	
Fetal/infant sex	Male infants are at increased risk for neonatal morbidity and mortality compared to female infants (45).	Male infants are at increased risk for preterm birth compared to female infants (46).	
Labour variables			
Cord complications	Umbilical cord complications are associated with perinatal mortality (47, 48).	n/a	
Non-reassuring fetal heart rate	Non-reassuring fetal heart rate is associated with low Apgar scores and NICU admission (49).	n/a	
Fetal distress	Fetal distress is associated with NICU admission (49).	n/a	

Variable	Association with neonatal morbidity (Chapter 3)	Association with early birth (Chapter 5)	Potential measurement issues
Labour onset	Caesarean section without labour is associated with neonatal morbidity and mortality (50).	n/a	
Forceps	Delivery by forceps is associated with poor neonatal outcomes, including hemorrhage (51, 52).	n/a	
Vacuum extraction	Delivery by vacuum extraction is associated with need for assisted ventilation (52, 53).	n/a	
Gestational age			
Gestational age	n/a	See literature review.	Misclassification of adjacent categories may occur which may be non-differential (digit preference) or differential (based on health status).
Neonatal outcomes			
NICU triage/admission	n/a	n/a	Triage/admission does not reflect mild morbidity. Decisions may reflect bed availability or precaution vs. morbidity per se.
Neonatal respiratory morbidity	n/a	n/a	The Discharge Abstract Database has relatively low sensitivity for neonatal outcomes vs. the Atlee Perinatal Database (54).

Table A.2. Description of Variables Included in Chapter 3 and Chapter 5 Analyses.

Variable	Description	Scale of measurement	
		Original	Analysis
Prenatal socio-demographic and lifestyle variables			
Maternal age	Mother's age at the time of infant's birth	Continuous (years)	<20 years, 20-34 years, ≥35 years
Maternal marital status	Mother's marital status at the time of infant's birth	Single; Divorced; Separated; Widowed; Common-Law; Married	Single; Divorced, separated, widowed; Common-Law; Married
Maternal income	Median neighbourhood income based on census information (Statistics Canada, 2006) on forward sortation area	n/a (Derived from postal code)	$50,000-$59,999; $60,000-$69,999; $70,000-$79,999; $80,000-$89,999; $90,000 or more
Parity	Number of previous live births (term or preterm)	Continuous (number)	Nulliparous (0); Primi/multiparous (1 or more)
Previous preterm delivery	Number of previous live births prior to 37 weeks gestation	Continuous (number)	Yes (1 or more); No
Previous abortion	Number of previous spontaneous or induced deliveries prior to 20 weeks gestation or less than 500 grams	Continuous (number)	Yes (1 or more); No
Prenatal care	Number of prenatal care visits attended by mother, where inadequate is defined as fewer than 4 visits by 36 weeks gestation	No prenatal care; Inadequate; Normal / adequate	None or inadequate; Adequate

Variable	Description	Scale of measurement	
		Original	Analysis
Smoking during pregnancy	Any smoking by the mother during pregnancy	Yes; No	Yes; No
Drug use during pregnancy	Prior to June, 2006: any illicit drug use by the mother during pregnancy; after June, 2006, use of cocaine, gas/glue, hallucinogens, marijuana, methadone, narcotics, amphetamines, or opioids	Yes; No	Yes (any); No
Alcohol use during pregnancy	Any or problematic alcohol use by the mother during pregnancy	Problem with alcohol; Any alcohol use; None	Yes (any); No
Biological determinants of preterm birth			
Infection and inflammation	Pregnancy affected by chorioamnionitis, bacterial vaginosis, systemic infection (fever); any of: tuberculosis, cytomegalovirus, parvovirus B19, C difficile, chickenpox, MRSA/VRE, hepatitis, HPV, HIV, herpes, or other STD; or premature rupture of the membranes	n/a (Derived)	Yes (1 or more); No
Placental ischemia and other hypoxia	Pregnancy affected by preeclampsia, eclampsia, chronic hypertension, gestational hypertension, small for gestational age (<5th percentile), placenta previa, placental abruption, other bleeding after 20 weeks, or vascular disease	n/a (Derived)	Yes (1 or more); No
Other biological determinants	Pregnancy affected by preexisting diabetes (type I or type II), gestational diabetes, polyhydramnios, or oligohydramnios	n/a (Derived)	Yes (1 or more); No

Variable	Description	Scale of measurement	
		Original	Analysis
Other pre-delivery covariates			
Other maternal medical conditions	Pre-existing conditions thought to present a risk to the pregnancy: anemia, autoimmune disease, connective tissue disorder, gastrointestinal disease, hematological disease, hormonal disease, renal disease, respiratory disease	n/a (Derived)	Yes (1 or more); No
Congenital anomalies	Major (life-threatening, disabling, or requiring major surgery, including chromosomal anomalies); minor	Major; Minor; None	Yes (any); No
Fetal/infant sex	Fetal sex as confirmed at birth	Male; Female	Male; Female
Labour variables			
Cord complications	Neck, knot, body, prolapsed, laceration, short, 2-vessel, velamentous, or other	Ordinal	Yes (1 or more); No
Non-reassuring fetal heart rate	Atypical, abnormal, late deceleration, variable deceleration, fetal bradycardia, fetal tachycardia, or decreased variability	Ordinal	Yes (any except variable decelerations); No
Fetal distress	Decreased movement, non-reactive non-stress test, abnormal biophysical profile, abnormal Doppler readings, or spontaneous decels	Ordinal	Yes (any); No
Labour onset	No labour (caesarean section before labour), induction of labour, or spontaneous	Ordinal	No labour; Induced labour; Spontaneous
Forceps	Use of forceps to deliver the infant (low forceps, mid forceps, forceps rotation, failed forceps, or breech delivery with forceps)	Ordinal	Yes (any); No

Variable	Description	Scale of measurement	
		Original	Analysis
Vacuum extraction	Use of vacuum extraction to deliver the infant	Yes; No	Yes; No
Gestational age			
Gestational age	Best obstetrical estimate using mother's last menstrual period (if within 4 days of ultrasound) or first trimester ultrasound (if last menstrual period estimate >4 days from first trimester ultrasound estimate	Continuous (weeks)	Late preterm (34-36 weeks); Early term (37-38 weeks); Full term (39-41 weeks)
Neonatal outcomes			
NICU triage/admission	Triage or admission of infant to the NICU (St. Joseph's Health Care) or special care nursery (London Health Sciences Centre-Victoria Hospital)	Ordinal	Admission; Triage; No admission/triage
Neonatal respiratory morbidity	ICD-10 codes: P22.0 (respiratory distress syndrome), P22.1 (transient tachypnea of the newborn), P22.8 (other respiratory distress of the newborn), P22.9 (respiratory distress of the newborn, unspecified), P27.1 (bronchopulmonary dysplasia), P29.3 (persistent pulmonary hypertension)	n/a (Derived)	Yes (1 or more); No

Table A.3. Definitions of Conditions Included in the Biological Determinants of Preterm Birth.

Condition	Definition
Infection and inflammation	
Bacterial vaginosis	Vaginal pH >4.5, creamy discharge, and foul odour.
Chorioamnionitis	Fever with sustained fetal or maternal tachycardia, uterine tenderness, or foul odour of amniotic fluid.
Other intrauterine or systemic infections	Maternal fever of 38^{o}C or higher on 3 readings over 6 hours.
Premature rupture of the membranes	Rupture of the membranes more than 24 hours prior to onset of labour.
Placental ischemia and other hypoxia	
Preeclampsia	Hypertension which develops after 20 weeks, proteinuria, and/or end organ involvement.
Eclampsia	Severe preeclampsia late in pregnancy or during delivery, with convulsions or coma.
Chronic hypertension	Hypertension prior to pregnancy or in the first 20 weeks of gestation.
Gestational hypertension	Diastolic blood pressure >90mmHg on at least 2 occasions after 20 weeks gestation (high blood pressure detected for first time in pregnancy); no proteinuria.
Small for gestational age	Birth weight less than 5th percentile for gestational age.
Placental previa	Placenta located over or near the internal os (total, partial, marginal, or low-lying).
Placental abruption	Premature separation of the placenta.
Other bleeding	Bleeding that occurs after 20 weeks gestation.
Vascular disease	Vascular embolism and/or thrombosis; deep vein thrombosis.
Endocrine triggers	
Depression	Mood disorder marked by low mood, energy, activity; sleep disturbances; reduced appetite; feelings of guilt, worthlessness.
Anxiety	Mood disorder marked by persistent nervousness, trembling, tension, sweating, dizziness.

Condition	Definition
Other biological determinants	
Preexisting diabetes	Diabetes mellitus present before pregnancy.
Gestational diabetes	Abnormal glucose tolerance with onset during pregnancy.
Polyhydramnios	Amniotic fluid index of greater than 24 to 25 cm (> 95^{th} or 97^{th} percentiles).
Oligohydramnios	Amniotic fluid index of 5 cm or less.

A.3 Data Management and Cleaning

A.3.1 Data Cleaning

Data from both the perinatal database and the Discharge Abstract Database were transferred to the author in Excel files. These files were uploaded into SAS 9.2 (55) for data cleaning and analysis. The PROC FREQ procedure was used to examine each variable for inappropriate characters and out-of-range values. Because inappropriate and implausible values could not be compared against the original chart, these were converted to missing values. However, because both datasets routinely undergo validation procedures, this was a rare occurrence. (Refer to Table A.4.)

A.3.2 Missing Data

The analyses required the assumption that data were missing completely at random (56, 57). Data in the perinatal database and the Discharge Abstract Database may be missing if (a) the physician or nurse did not record the variable of interest in the chart or (b) the data abstractor did not enter the variable of interest into the database.

Table A.4 shows the percentage of missing data for each variable. Note that for some variables, it was impossible to determine the percentage of records that had missing values because a value was only entered if the condition was present. In other words, for these variables, records with “missing” values included all patients who did not have the condition as well as patients for whom information was truly missing. In the perinatal database, these variables included infections, maternal medical conditions, non-reassuring fetal heart rate, and fetal distress. This was also the case for the respiratory morbidity variable in the Discharge Abstract Database. It was therefore impossible to determine the rate of true missingness for these variables.

Table A.4. Missing and Implausible Values for Variables Included in Chapter 3 and Chapter 5.

Variable	Missing N (%)	Implausible N (%)	Decisions re. implausible values
Prenatal socio-demographic and lifestyle variables			
Maternal age	0 (0.0)	0 (0.0)	-1 coded as missing
Maternal marital status	14 (0.0)	0 (0.0)	---
Forward sortation area (for median neighbourhood income)	0 (0.0)	0 (0.0)	---
Previous term delivery	0 (0.0)	0 (0.0)	---
Previous preterm delivery	0 (0.0)	0 (0.0)	---
Previous abortion	1 (0.0)	4 (0.0)	>20 coded with other multiple abortions as 1/>
Prenatal care	0 (0.0)	0 (0.0)	---
Smoking during pregnancy	0 (0.0)	1 (0.0)	-1 coded as missing
Drug use during pregnancy	1 (0.0)	51 (0.1)	-1 coded as missing
Alcohol during pregnancy	0 (0.0)	3 (0.0)	-1 coded as missing
Biological determinants of preterm birth			
Infection and inflammation			
Chorioamnionitis	0 (0.0)	0 (0.0)	---
Infection (incl. bacterial vaginosis)	n/a	1 (0.0)	0 coded as missing
Other infection (fever)	1 (0.0)	0 (0.0)	---
Premature rupture of the membranes	1 (0.0)	0 (0.0)	---
Placental ischemia and other hypoxia			
Pregnancy hypertension (incl. preeclampsia, eclampsia, gestational hypertension)	9 (0.0)	0 (0.0)	---
Chronic hypertension	0 (0.0)	0 (0.0)	---
Birth weight (for size for gestational age)	2 (0.0)	54 (0.1)	BW >4 SD below/above median sex-specific BW for GA coded as missing
Placenta previa	7 (0.0)	0 (0.0)	---
Placental abruption	95 (0.2)	0 (0.0)	---
Other bleeding >20 weeks	1 (0.0)	28 (0.1)	-1 coded as missing
Vascular disease	n/a	0 (0.0)	---
Other biological determinants			
Diabetes mellitus (incl. preexisting and gestation diabetes)	3 (0.0)	0 (0.0)	---
Polyhydramnios	0 (0.0)	3 (0.0)	-1 coded as missing
Oligohydramnios	0 (0.0)	5 (0.0)	-1 coded as missing
Other pre-delivery covariates			
Maternal medical conditions	n/a	1 (0.0)	0 coded as missing

Variable	Missing N (%)	Implausible N (%)	Decisions re. implausible values
Congenital anomalies	6 (0.0)	0 (0.0)	---
Fetal/infant sex	0 (0.0)	0 (0.0)	---
Labour variables			
Cord complications	18 (0.1)	2 (0.0)	Symbols coded as missing
Non-reassuring fetal heart rate	n/a	4 (0.0)	0, 6, X coded as missing
Fetal distress	n/a	15 (0.0)	Character values coded as missing
Labour onset	2 (0.0)	0 (0.0)	---
Forceps	84 (0.2)	0 (0.0)	---
Vacuum extraction	4 (0.0)	0 (0.0)	---
Gestational age			
Gestational age in weeks	0 (0.0)	0 (0.0)	---
Chapter 3 Outcomes			
NICU triage/admission	0 (0.0)	0 (0.0)	---
Respiratory morbidity			
Respiratory distress syndrome	n/a	0 (0.0)	---
Transient tachypnea of the newborn	n/a	0 (0.0)	---
Other respiratory distress of the newborn	n/a	0 (0.0)	---
Respiratory distress of the newborn, unspecified	n/a	0 (0.0)	---
Bronchopulmonary dysplasia	n/a	0 (0.0)	---
Persistent pulmonary hypertension	n/a	0 (0.0)	---

* Because cleaning was done prior to derivation of the study sample from the study population, these results apply to the analyses in both Chapter 3 and Chapter 5.

A.4 Statistical Analyses

A.4.1 Modified Poisson Regression

Modified Poisson regression (58) provides a direct estimate of the relative risk of the dependent variable. Direct estimation of the relative risk is preferred in cohort studies due to inaccuracy of the odds ratio in estimating the relative risk in the presence of common outcomes or variable baseline risk in subgroups (59, 60). Although binomial regression and Poisson regression can also be used to directly estimate the relative risk, these approaches are limited, respectively, by convergence problems and overestimation of the standard error. Modified Poisson regression, which is performed using SAS PROC GENMOD with a log link function, has the advantage of producing a robust standard error using "sandwich" estimation (58). (Sandwich estimation corrects for misspecification of the error term under the binomial distribution.) The general equation (58) for the log likelihood of the outcome is as follows:

$$l(\alpha, \beta) = C \cdot \sum_{i=1}^{n} [y_i (\alpha + \beta x_i) - \exp(\alpha + \beta x_i)]$$

(Equation A1)

where:

y Is the outcome, with a Poisson distribution (1 = event, 0 = no event).

x Is the exposure (1 = exposed; 0 = unexposed).

C Is a constant.

exp(β) Is the relative risk of the outcome.

A.4.2 Blockwise Model Building

Blockwise procedures are essentially stepwise selection (a combination of backward elimination and forward selection) with blocks of covariates. Forward selection is applied to blocks of covariates, and backward selection is applied within blocks. For example, variables in Block 1 of the conceptual model are entered into the model as a group. Variables within this block are taken out until all variables have a p-value of <.20. Then, the Block 2 variables are added and the same process is repeated. Note that at each stage,

variables in a previous block can be taken out of the model if their p-value exceeds .20. This process is repeated until all blocks have been entered into the model.

An advantage of blockwise regression is that it gives the researcher greater control over the model building process. Rather than relying on purely automated variable selection, variables are entered in a particular order based on theory. In the case of this thesis, variables were grouped according to conceptual commonalities and entered into the model according to temporality, from distal to proximal.

A.4.3 Measures to Address Non-Independence

Statistical models assume independence among observations (56). However, repeated births to the same mother tend to be more alike than births to different mothers. This results in non-independence among observations. If non-independence is ignored, the variance tends to be underestimated (56), and tests of statistical significance may be too liberal (56, 57). Two methods were used to address non-independence among observations in the perinatal database (i.e., for the analyses described in Chapter 3 and Chapter 5).

In Chapter 3, non-independence in the modified Poisson regression models was addressed using generalized estimating equations (**GEE**) (62). GEE assumes a "working" correlation structure for non-independent observations. The correlation is then taken into account using robust sandwich-type variance estimation. GEE has four possible working correlation structures: independence, exchangeable, autoregressive, and unbounded. The model tends to be robust regardless of the choice of correlation structure (56). Modified Poisson regression can be extended to accommodate GEE using a cluster identifier (i.e., the mother's chart number) in the REPEATED statement and by specifying the working correlation structure (62). Although the exchangeable structure is more commonly used (56), the independence structure was used in this study to accommodate tests of mediation (63). However, results are robust to the type of correlation structure used (56).

In Chapter 5, one birth per mother was randomly selected for analysis using SAS PROC SURVEYSELECT with maternal chart number in the BY statement, since statistical

methods of accounting for non-independence were not compatible with multinomial logistic regression. (See Appendix A.4.7.) By using random selection, this subsample was representative of the larger group of spontaneous births.

A.4.4 Mediation

Baron and Kenny define a mediator as a "third variable" through which an exposure influences an outcome (64). Previous approaches to testing mediation have (a) tested the impact of the mediator on the magnitude of the exposure-outcome relationship with no measure of the indirect effect of the exposure (65, 66) or (b) tested the indirect effect of the exposure with inaccurate estimation of the standard error (67). Schluchter (63) used GEE to accurately estimate the standard error for the indirect effect of the exposure. This indirect effect is calculated by testing the difference between coefficients in a full model (i.e., with the mediator) and a reduced model (i.e., without the mediator). This is accomplished by creating a dataset with two records per observation (with additional variables G [0, 1] and M [0, M], where G identifies the record and M identifies the mediator dummy variables):

	Y	X_1	X_2	…	X_p	G	M*
Record 1	y_i	x_{i1}	x_{i2}	…	x_{ip}	0	0
Record 2	y_i	x_{i1}	x_{i2}	…	x_{ip}	1	m_i

A model containing the terms for covariates (X_i, G, M_i, $G*X_i$ interactions) is created:

Model: $g(E(Y \mid X_1, \ldots, X_p, G, M^*) = \beta_0 + \beta_1 X_1 + \ldots + \beta_p X_p + \theta_0 G + \theta_1 G \cdot X_1 + \ldots + \theta_p G \cdot X_p + \gamma M^*$

(Equation A2)

The two records for each observation (in this case, each infant) are treated as a cluster by specifying an identifier (in this case, maternal chart number) in the REPEATED statement of PROC GENMOD. (Accounting for clustering at the highest level [i.e., the mother] automatically accounts for clustering at a lower level [i.e., the infant].) An independence working correlation structure is specified, and robust variance estimates are produced using "sandwich" estimation. Inclusion of the $G*X_i$ interaction(s) in the above

model "tricks" SAS into producing regression coefficients that reflect coefficients in the full model and the reduced model:

Full: $g(E(Y \mid X_1, \ldots, X_p, M^* = M, G = 1))$

$= \beta_0 + \beta_1 X_1 + \ldots + \beta_p X_p + \theta_0 + \theta_1 X_1 + \ldots + \theta_p X_p + \gamma M$

$= (\beta_0 + \theta_0) + (\beta_1 + \theta_1) X_1 + \ldots + (\beta p_1 + \theta_p) X_p + \gamma M$

(Equation A3)

Reduced: $g(E(y \mid X_1, \ldots, X_p, M^* = 0, G = 0))$

$= \beta_0 + \beta_1 X_1 + \ldots + \beta_p X_p$

(Equation A4)

When G=1 and M=M, Equation A2 reduces to Equation A3. Moreover, when G=0 and M=0, Equation A2 reduces to Equation A4. The coefficient for the G^*X_i interaction term(s) in Equation A2 can therefore be interpreted as the indirect effect(s) ($\theta_i = \beta - \beta^*$) (63). (Note that Schluchter's method accommodates multiple exposures, multiple mediators, and categorical mediators and outcomes, making it ideal for this study.)

A.4.5 Moderation

Baron and Kenny define a moderator as a "third variable" that affects the strength or direction of the effect of an exposure on an outcome (64). A distinction can be made between statistical and biological interaction. Statistical interaction refers only to the inclusion of an interaction term in a statistical model; in contrast, biological interaction describes the "interdependent action" of two covariates to cause (or prevent) an outcome (68, 69). Statistical interaction is not always a true reflection of biological interaction.

Interaction can be assessed on the multiplicative scale or on the additive scale. Multiplicative interaction is said to be present when the joint effect of two covariates is different from the product of their individual effects. Additive interaction is present when the joint effect of two covariates differs from the sum of their individual effects (68). Rothman (70, 71) demonstrated biological interaction in his sufficient cause model: biological interaction between two covariates exists when at least one of the sufficient causes of an outcome requires both covariates. This framing implies an additive model;

for this reason, Rothman (70, 71) and others (68, 69, 72) argue that additive interaction more closely approximates biological interaction than multiplicative interaction.

Additive interaction can be tested by calculating the relative excess risk due to interaction (**RERI**) (73). Interaction terms between the covariates of interest are added to the multivariable regression model. These interaction terms produce values on the multiplicative scale which are then used to calculate the RERIs:

$$RERI = RR_{11} - RR_{10} - RR_{01} + 1$$

(Equation A5)

where:

RR_{11} Is the relative risk for the interaction term between Covariate 1 and Covariate 2.

RR_{10} Is the relative risk for Covariate 1.

RR_{01} Is the relative risk for Covariate 2.

Several pieces of output are then gathered and inserted into SAS code to calculate 95% confidence intervals. These included betas, variances, and covariances for each of the parameters listed in Equation A5. Confidence intervals are calculated using the method of variance estimates recovery (**MOVER**) technique (73). Rather than forcing confidence intervals to be symmetric, the MOVER technique "recovers" variance estimates needed to calculate more accurate (i.e., asymmetric) confidence intervals (73). (Note that the use of relative risks to assess additive interaction is preferred to odds ratios because odds ratios can exaggerate the effect of additive interaction, particularly when covariates are adjusted for (73).)

A.4.6 Moderated Mediation

James and Brett (74) introduced the term "moderated mediation" to describe the situation in which a mediated relationship involves a moderator. Although their primary example involved an exposure, outcome, mediator, and (separate) moderator, they acknowledged that in some cases, the exposure and mediator may interact to cause an outcome (74). Likewise, Judd and Kenny (65) and Preacher et al. (75) suggested that it is possible for an exposure to affect an outcome partially by altering the effect of the mediator, depending

on the level of the exposure. An exposure-mediator interaction may provide insight into how (mediation) and when (moderation) an exposure causes an effect (65, 75).

Ananth et al. (76) give an example of a situation in which it is biologically plausible that both mediation and moderation exist. They hypothesized that placental abruption and preterm delivery could interact to produce excess risk for perinatal mortality, and that, logically, preterm birth is also a partial mediator in the association between placental abruption and perinatal mortality.

Methods for testing moderated mediation have only recently moved from theoretical (77) to practical (75, 78, 79), and there are limitations to these new techniques. Robins and Greenland (77) argued that when the exposure and mediator interact, the direct and indirect effects of the exposure cannot be separated and recommended stratifying on the mediator and examining the effect of the exposure that remains at each level. Preacher et al. (75) proposed methods by which "conditional indirect effects" can be tested using a product of coefficients approach; however, their methods allow only for continuous mediators and outcomes. Most recently, VanderWeele (76, 79, 80) used counterfactual theory to allow for and test mediation in the presence of interaction. SAS and SPSS macros calculate controlled direct effects, natural direct and indirect effects, and total effects and allow for binary mediators and outcomes. However, for calculation of relative risks, the macro has only been extended to log-linear models and, in addition to not allowing for use of modified Poisson regression, has convergence problems and a complex interpretation. The macro is also inflexible in that it does not allow for polytomous mediators, multiple exposures, or clustering among observations (challenges presented by the thesis).

However, despite the inability to use the most up-to-date methods, theory provided by early work on this topic (e.g., James and Brett (74), Judd and Kenny (65)) holds. Judd and Kenny (65), for example, suggested first examining mediation. If there is mediation (or even if there is not mediation), moderation can next be examined to determine whether the exposure "exerts its effect, in part, by altering the causal parameters of the process model" (pg. 614) (65). This was the approach taken by the thesis.

A.4.7 Multinomial Logistic Regression

Multinomial logistic regression is an extension of binary logistic regression that allows for more than two categories in the dependent variable. Like binary logistic regression, multinomial logistic regression uses maximum likelihood estimation to estimate the probability of category membership in the dependent variable relative to a base category. Although multinomial logistic regression is intended for nominal outcomes, it can be used for ordinal outcomes when the order of the categories is not of interest (81). Unlike ordinal logistic regression (which allows for ordinal dependent variables), multinomial logistic regression does not require strict assumptions such as the proportional odds assumption. However, there are several assumptions that must be met: (a) independence among dependent variable categories (i.e., membership in one category cannot be related to membership in another category); and (b) non-perfect separation (i.e., categories of the outcome variable cannot be perfectly separated by predictor(s)) (82, 83). Multinomial logistic regression is performed using SAS PROC LOGISTIC with a generalized logit link function. The general equation for the conditional probability in a three category model is (81):

$$P(Y = j|x) = \frac{e^{g_j(x)}}{\sum_{k=0}^{2} e^{g_i(x)}}$$

(Equation A6)

where:

y Is the outcome, with possible categories j = 0, 1, 2.

x Is the exposure (1 = exposed; 0 = unexposed).

g Is a constant.

A.5 Frequencies of Components of Derived Variables

Several variables in the analyses for Chapter 3 and Chapter 5 were composites of variables thought to reflect the same underlying concept. The following tables show the frequencies of the components of each of the derived variables. These tables contain information on the biological determinants of preterm birth (Table A.5), other maternal medical conditions (Table A.6), and NICU triage/admission and neonatal respiratory morbidity (Table A.7).

Table A.5. Prevalence of Conditions Included in the Biological Determinants of Preterm Birth in the Chapter 3 Sample (N=38,807) and Chapter 5 Sample (N=17,678).

	Chapter 3 sample		Chapter 5 sample	
	N	%	N	%
Infection and inflammation				
Chorioamnionitis				
Yes	406/38,807	1.1	176/17,678	1.0
No	38,401/38,807	98.9	17,502/17,678	99.0
Bacterial vaginosis				
Yes	93/38,807	0.2	36/17,678	0.2
No	38,714/38,807	99.8	17,642/17,678	99.8
Fever				
Yes	869/38,806	2.2	331/17,678	1.9
No	37,937/38,806	97.8	17,347/17,678	98.1
Cytomegalovirus				
Yes	3/38,807	0.0	1/17,678	0.0
No	38,804/38,807	100.0	17,677/17,678	100.0
HPV				
Yes	125/38,807	0.3	48/17,678	0.3
No	38,682/38,807	99.7	17,630/17,678	99.7
HIV				
Yes	18/38,807	0.1	8/17,678	0.1
No	38,789/38,807	99.9	17,670/17,678	99.9
Parvovirus B19				
Yes	24/38,807	0.1	9/17,678	0.1
No	38,783/38,807	99.9	17,669/17,678	99.9
Tuberculosis				
Yes	13/38,807	0.0	3/17,678	0.0
No	38,794/38,807	100.0	17,675/17,678	100.0
Herpes				
Yes	507/38,807	1.3	204/17,678	1.2
No	38,300/38,807	98.7	17,474/17,678	98.8
Hepatitis				
Yes	252/38,807	0.7	110/17,678	0.6
No	38,555/38,807	99.3	17,568/17,678	99.4
C difficile				
Yes	3/38,807	0.0	1/17,678	0.0
No	38,804/38,807	100.0	17,677/17,678	100.0
Chickenpox				
Yes	20/38,807	0.1	6/17,678	0.0
No	38,787/38,807	99.9	17,672/17,678	100.0
MRSA/VRE				
Yes	44/38,807	0.0	1/17,678	0.0
No	38,803/38,807	100.0	17,677/17,678	100.0

	Chapter 3 sample		Chapter 5 sample	
	N	%	N	%
Other STD				
Yes	257/38,807	0.7	126/17,678	0.7
No	38,550/38,807	99.3	17,552/17,678	99.3
Premature rupture of the membranes				
Yes	421/38,806	1.1	148/17,677	0.8
No	38,385/38,806	98.9	17,529/17,677	99.2
Placental ischemia and other hypoxia				
Preeclampsia				
Yes	1,029/38,799	2.7	110/17,676	0.6
No	37,770/38,799	97.3	17,566/17,676	99.4
Eclampsia				
Yes	9/38,799	0.0	3/17,676	0.0
No	38,790/38,799	100.0	17,673/17,676	100.0
Chronic hypertension				
Yes	376/38,807	1.0	73/17,678	0.4
No	38,431/38,807	99.0	17,605/17,678	99.6
Gestational hypertension				
Yes	2,051/38,799	5.3	521/17,676	3.0
No	36,748/38,799	94.7	17,155/17,676	97.0
Small for gestational age				
Yes	1,473/38,751	3.8	619/17,678	3.5
No	37,278/38,751	96.2	17,059/17,678	96.5
Placenta previa				
Yes	193/38,800	0.5	40/17,676	0.2
No	38,607/38,800	99.5	17,636/17,676	99.8
Placental abruption				
Yes	471/38,712	1.2	198/17,634	1.1
No	38,241/38,712	98.8	17,436/17,634	98.9
Other bleeding <20 weeks				
Yes	3,357/38,778	8.7	1,450/17,666	8.2
No	35,421/38,778	91.3	16,216/17,666	91.8
Vascular disease				
Yes	184/38,807	0.5	60/17,678	0.3
No	38,623/38,807	99.5	17,618/17,678	99.7
Other biological determinants of preterm birth				
Preexisting diabetes				
Yes	255/38,804	0.7	34/17,677	0.2
No	38,549/38,804	99.3	17,643/17,677	99.8
Gestational diabetes				
Yes	1,885/38,804	4.9	515/17,677	2.9
No	36,919/38,804	95.1	17,162/17,677	97.1

	Chapter 3 sample		Chapter 5 sample	
	N	%	N	%
Polyhydramnios				
Yes	382/38,804	0.9	92/17,675	0.5
No	38,422/38,804	99.1	17,583/17,675	99.5
Oligohydramnios				
Yes	727/38,802	1.9	77/17,676	0.4
No	38,075/38,802	98.1	17,599/17,676	99.6

Table A.6. Prevalence of Conditions Included in Other Maternal Medical Conditions in the Chapter 3 Sample (N=38,807) and Chapter 5 Sample (N=17,678).

	Chapter 3 sample		Chapter 5 sample	
	N	%	N	%
Anemia				
Yes	2,183/38,807	5.6	880/17,678	5.0
No	36.624/38,807	94.4	16,798/17,678	95.0
Autoimmune disease				
Yes	18/38,807	0.1	8/17,678	0.1
No	38,789/38,807	99.9	17,670/17,678	99.9
Connective tissue disease				
Yes	170/38,807	0.4	66/17,678	0.4
No	38,637/38,807	99.6	17,612/17,678	99.6
Hormonal disease				
Yes	1,862/38,807	4.8	711/17,678	4.0
No	36,945/38,807	95.2	16,967/17,678	96.0
Gastrointestinal disease				
Yes	1,784/38,807	4.6	546/17,678	3.1
No	37,023/38,807	95.4	17,132/17,678	96.9
Hematological disease				
Yes	497/38,807	1.3	168/17,678	1.0
No	38,310/38,807	98.7	17,510/17,678	99.0
Renal disease				
Yes	491/38,807	1.3	172/17,678	1.0
No	38,316/38,807	98.7	17,506/17,678	99.0
Respiratory disease				
Yes	3,383/38,807	8.7	1,309/17,678	7.4
No	35,424/38,807	91.3	16,369/17,678	92.6

Table A.7. Prevalence of Outcomes Included in Neonatal Outcome Variables in the Chapter 3 Sample (N=38,807).

	N	%
NICU triage/admission		
NICU triage/admission		
NICU admission	1,515/38,807	3.9
NICU triage	1,149/38,807	3.0
No triage or admission	36,143/38,807	93.1
Neonatal respiratory morbidity		
Respiratory distress syndrome		
Yes	79/38,807	0.2
No	38,728/38,807	99.8
Transient tachypnea of the newborn		
Yes	836/38,807	2.2
No	37,971/38,807	97.8
Other respiratory distress of the newborn		
Yes	314/38,807	0.8
No	38,493/38,807	99.2
Respiratory distress of the newborn, unspecified		
Yes	196/38,807	0.5
No	38,611/38,807	99.5
Bronchopulmonary dysplasia		
Yes	2/38,807	0.0
No	38,805/38,807	100.0
Persistent pulmonary hypertension		
Yes	24/38,807	0.1
No	38,783/38,807	99.9

A.6 Multicollinearity Analyses for Chapter 3 and Chapter 5

Prior to multivariable analyses, multicollinearity was assessed using two approaches. First, correlations among the covariates were examined. Because all covariates were categorical, Pearson correlation coefficients could not be used. Instead, polychoric correlations were calculated. Polychoric correlations are an approach to testing correlations among ordinal variables (84). An assumption is made that the ordinal data come from a normally distributed underlying variable X^* with a range from negative infinity to positive infinity. The categories in ordinal variable X correspond to thresholds in normally distributed underlying variable X^* (84). Polychoric correlations are interpreted in the same manner as Pearson's correlations, with values greater than 0.50 signifying a moderate or high correlation. The results of this analysis showed that there were several relationships which had moderate correlations or higher: smoking during pregnancy and marital status; drug use during pregnancy and marital status, prenatal care, and smoking during pregnancy; and alcohol use during pregnancy and smoking or drug use during pregnancy. See Table A.8.

Therefore, to further test for multicollinearity, multivariable regression models with collinearity diagnostics were produced. Tests for multicollinearity have not been developed for binary outcomes as they have for continuous outcomes (i.e., PROC REG options VIF and TOL). However, because it is the relationships among covariates that are of interest, rather than the relationships between the covariates and the outcome, multicollinearity can be tested using PROC REG and substituting in a continuous outcome. Therefore, we assessed multicollinearity with PROC REG VIF and TOL, using birth weight as a substitute continuous outcome.

As can be seen in Table A.9, none of the values in the current study exceeded allowable thresholds. We therefore concluded that there was no multicollinearity and that all covariates could be included in the multivariable model. Note that because the covariates included in the Chapter 5 analyses were a subset of those used in Chapter 3, we did not repeat multicollinearity tests for both chapters.

Table A.8. Polychoric Correlations among Covariates for Chapter 3 and Chapter 5 Analyses (**bold** = moderate or greater).

	1	2	3	4	5	6	7	8	9	10
1		-0.46	-0.17	-0.39	0.15	0.20	-0.24	-0.29	-0.31	-0.19
2			0.17	0.21	0.01	0.07	0.49	**0.61**	**0.55**	0.43
3				0.03	0.04	0.04	0.22	0.30	0.23	0.15
4					-0.21	-0.21	-0.10	0.01	0.08	0.16
5						0.18	0.08	0.12	0.08	-0.03
6							0.03	0.16	0.12	0.07
7								0.46	**0.60**	0.42
8									**0.66**	**0.50**
9										**0.65**
10										

	11	12	13	14	15	16	17	18	19
1	-0.08	0.05	0.16	0.05	0.02	-0.05	-0.04	0.04	0.00
2	0.15	0.00	-0.04	0.01	-0.02	-0.03	0.02	0.02	-0.01
3	0.04	0.00	0.00	0.00	-0.01	-0.02	-0.06	0.02	0.01
4	0.23	0.13	0.00	-0.02	0.00	0.44	0.27	-0.05	0.01
5	-0.05	0.09	0.14	0.09	0.00	-0.15	-0.07	0.33	0.00
6	0.04	0.03	0.06	0.05	0.00	-0.04	0.02	0.03	-0.01
7	0.13	0.00	0.01	0.00	0.00	-0.07	-0.09	0.12	0.03
8	0.13	0.03	0.00	0.05	0.02	-0.10	0.00	0.06	-0.01
9	0.26	0.07	0.00	0.08	-0.01	-0.08	0.02	0.13	-0.04
10	0.19	0.05	0.03	0.03	0.02	-0.01	0.09	0.06	0.00
11		0.08	0.06	0.08	0.02	0.12	0.02	-0.01	0.02
12			0.19	0.18	0.08	0.02	0.04	0.23	0.01
13				0.16	0.02	0.01	-0.05	0.32	0.00
14					0.04	-0.02	0.04	0.09	-0.01
15						-0.06	-0.07	0.11	-0.01

	11	12	13	14	15	16	17	18	19
16							-0.03	-0.15	0.05
17								-0.05	0.08
18									0.03
19									

1 = maternal age, 2 = maternal marital status, 3 = median neighbourhood income, 4 = parity, 5 = previous preterm delivery, 6 = previous abortion, 7 = prenatal care, 8 = smoking during pregnancy, 9 = drug use during pregnancy, 10 = alcohol use during pregnancy, 11 = infection and inflammation, 12 = placental ischemia and other hypoxia, 13 = other biological determinants, 14 = other maternal medical conditions, 15 = cord complications, 16 = forceps, 17 = vacuum extraction, 18 = gestational age, 19 = infant sex.

Table A.9. Variance Inflation Factor, Tolerance, Eigenvalue, and Condition Index for Covariates for Chapter 3 and Chapter 5 Analyses.

Variable[1]	Variance Inflation Factor [2]	Tolerance[3]	Eigenvalue[4]	Condition index[5]
Intercept	.	0	.	.
Young maternal age	0.82	1.22	2.14	1.00
Old maternal age	0.93	1.07	1.58	1.17
Single marital status	0.71	1.41	1.48	1.20
Divorced, separated, widowed	0.98	1.02	1.30	1.29
Common-law	0.85	1.18	1.24	1.32
$50,000-$59,999 income	0.28	3.54	1.19	1.34
$60,000-$69,999 income	0.24	4.20	1.15	1.37
$70,000-$79,999 income	0.35	2.84	1.15	1.37
$80,000-$89,999 income	0.36	2.75	1.06	1.42
Nulliparity	0.83	1.20	1.03	1.44
Previous preterm delivery	0.93	1.08	1.00	1.46
Previous abortion	0.96	1.05	1.00	1.47
No or inadequate prenatal care	0.94	1.07	0.98	1.48
Smoking during pregnancy	0.78	1.29	0.96	1.49
Drug use during pregnancy	0.85	1.17	0.95	1.50
Alcohol use during pregnancy	0.92	1.08	0.93	1.52
Infection and inflammation	0.98	1.02	0.92	1.53
Placental ischemia and other hypoxia	0.96	1.04	0.91	1.54
Other biological determinants	0.96	1.04	0.89	1.55
Other maternal medical conditions	0.98	1.02	0.84	1.59
Cord complications	0.99	1.01	0.73	1.71
Forceps	0.96	1.05	0.71	1.73
Vacuum extraction	1.00	1.00	0.69	1.76
Late preterm	0.94	1.07	0.62	1.86
Early term	0.94	1.06	0.46	2.15
Male sex	1.00	1.00	0.09	4.85

[1] Only the level of the dummy variable under analysis is shown (e.g., “full term gestational age” not shown).
[2] Measures the inflation in the variances of the parameter estimates due to collinearities among predictors; >10 = problematic.
[3] = 1 / VIF; measures the tolerance values for parameter estimates and reflects the degree of multicollinearity; <0.10 = problematic.
[4] The variance of the covariates; Near 0 = problematic.
[5] The square root of ratio of the largest eigenvalue to each individual eigenvalue; reflects the instability in the model; >10 = problematic.

A.7 Additional Analyses for Chapter 3

A.7.1 Regression Diagnostics

Regression diagnostics were performed to test for outliers and influential observations in the final multivariable models for Chapter 3. Because regression diagnostic procedures have not been developed for modified Poisson regression, these were performed using logistic regression.

The confidence interval displacement statistic (C statistic) is analogous to Cook's Distance statistic for linear regression and provides a measure of the influence of an individual observation on the regression parameter estimate. A C statistic is calculated for each observation; any observation with a value >1 is influential (85). The DFbeta is the standardized difference in a parameter estimate after deleting an observation compared to prior. DFbetas are computed for each observation for each parameter estimate. A DFbeta >2 is considered to indicate an influential observation (85).

Results for the DFbetas are in Table A.10. For NICU triage/admission, C statistic values ranged from <0.01 to 0.01. For neonatal respiratory morbidity, C statistic values ranged from <0.01 to 0.11. Because no values were influential, no observations were deleted.

A.7.2 Model Building Steps

The steps used to perform blockwise model building are shown in Table A.11 (NICU triage/admission) and Table A.12 (neonatal respiratory morbidity).

A.7.3 Mediation Analysis Details

Schluchter's method for testing mediation (66) produces a multivariable model with indirect effects denoted by $G*X_i$. Because the indirect effects of only the biological determinants of preterm birth were of interest, these are presented in Chapter 3. The full results of the generalized estimating equations (**GEE**) model are presented in Table A.13 (NICU triage/admission) and Table A.14 (neonatal respiratory morbidity). For simplicity, only the categories of interest (not the reference categories) are presented.

A.7.4 Addition of Labour Variables to Multivariable Models

Labour onset, non-reassuring fetal heart rate, and fetal distress were considered to be pathway variables and were therefore not included in the multivariable models for Chapter 3. However, we acknowledge that it may be important to estimate the effects of the biological determinants of preterm birth and gestational age above and beyond the intermediary effects of these labour variables. Therefore, as a sensitivity analysis, we controlled for labour onset, non-reassuring fetal heart rate, and fetal distress in the multivariable analyses of NICU triage/admission (Table A.15) and neonatal respiratory morbidity (Table A.16). The results showed that the adjusted relative risks for biological determinants of preterm birth and gestational age remained statistically significant after controlling for these labour variables. There was one exception to this: The impact of other biological determinants of preterm birth on neonatal respiratory morbidity was not statistically significant after adding labour variables to the model.

Table A.10. DFbetas for Final Neonatal Outcomes Multivariable Models (Chapter 3).

	Range	No. >2
NICU triage/admission		
Young maternal age	-0.06, 0.09	0
Old maternal age	-0.04, 0.05	0
Nulliparous	-0.05, 0.03	0
No or inadequate prenatal care	-0.09, 0.12	0
Smoking during pregnancy	-0.05, 0.05	0
Drug use during pregnancy	-0.08, 0.09	0
Infection and inflammation	-0.04, 0.05	0
Placental ischemia and other hypoxia	-0.03, 0.04	0
Other biological determinants	-0.05, 0.06	0
Maternal medical conditions	-0.02, 0.04	0
Cord complications	-0.03, 0.03	0
Vacuum extraction	-0.12, 0.16	0
Late preterm gestational age	-0.04, 0.04	0
Early term gestational age	-0.03, 0.04	0
Male sex	-0.03, 0.02	0
Neonatal respiratory morbidity		
Single marital status	-0.03, 0.06	0
Divorced, separated, or widowed	-0.08, 0.28	0
Common-law	-0.06, 0.07	0
Nulliparous	-0.04, 0.04	0
No or inadequate prenatal care	-0.07, 0.18	0
Drug use during pregnancy	-0.07, 0.15	0
Alcohol use during pregnancy	-0.07, 0.23	0
Infection and inflammation	-0.03, 0.08	0
Placental ischemia and other hypoxia	-0.03, 0.06	0
Other biological determinants	-0.03, 0.08	0
Late preterm gestational age	-0.04, 0.05	0
Early term gestational age	-0.04, 0.05	0
Male sex	-0.04, 0.03	0

* Only the level of the dummy variable under analysis is shown (e.g., “full term gestational age” not shown).

Table A.11. Model Building Steps for NICU Triage/admission Multivariable Model (Chapter 3).

	Univar. RR (p)	Block 1 RR (p)	Block 2 RR (p)	Block 3 RR (p)	Block 4 RR (p)	Block 5 RR (p)	Block 6 RR (p)
Prenatal socio-demographic and lifestyle variables							
Maternal age							
<20 years	1.20 (.01)	0.76 (<.01)	0.82 (.03)	0.86 (.09)	0.87 (.09)	0.91 (.28)	0.91 (.25)
20-34 years							
≥35 years	1.13 (.03)	1.28 (<.01)	1.17 (<.01)	1.16 (<.01)	1.16 (<.01)	1.13 (.01)	1.12 (.02)
Maternal marital status							
Single (never married)	1.38 (<.01)	1.08 (.23)	1.07 (.25)				
Widowed, separated, divorced	1.21 (.27)	1.07 (.70)	1.01 (.98)				
Common-law	1.12 (.03)	0.98 (.73)	0.98 (.73)				
Married							
Median neighbourhood family income							
$50,000-$59,999	1.14 (.12)	1.03 (.74)					
$60,000-$69,999	1.03 (.69)	1.01 (.91)					
$70,000-$79,999	0.98 (.81)	0.96 (.67)					
$80,000-$89,999	0.91 (.28)	0.91 (.35)					
$90,000 or more							
Parity							
Nulliparous	1.39 (<.01)	1.56 (<.01)	1.39 (<.01)	1.39 (<.01)	1.37 (<.01)	1.32 (<.01)	1.31 (<.01)
Primi/multiparous							
Previous preterm delivery							
Yes	1.45 (<.01)	1.70 (<.01)	1.54 (<.01)	1.53 (<.01)	1.52 (<.01)	1.01 (.85)	
No							
Previous abortion (spontaneous or induced)							
Yes	1.02 (.64)	0.98 (.67)					
No							

	Univar. RR (p)	Block 1 RR (p)	Block 2 RR (p)	Block 3 RR (p)	Block 4 RR (p)	Block 5 RR (p)	Block 6 RR (p)
Prenatal care							
None / inadequate	2.87 (<.01)	1.90 (<.01)	1.89 (<.01)	1.95 (<.01)	1.93 (<.01)	1.60 (<.01)	1.59 (<.01)
Normal / adequate							
Smoking during pregnancy							
Yes	1.42 (<.01)	1.14 (.02)	1.10 (.07)	1.12 (.02)	1.12 (.02)	1.07 (.16)	1.07 (.15)
No							
Drug use during pregnancy							
Yes	3.40 (<.01)	2.79 (<.01)	2.40 (<.01)	2.39 (<.01)	2.41 (<.01)	2.10 (<.01)	2.12 (<.01)
No							
Alcohol during pregnancy							
Yes	1.68 (<.01)	0.88 (.31)					
No							
Biological determinants of preterm birth							
Infection and inflammation							
Yes	2.44 (<.01)		2.20 (<.01)	2.21 (<.01)	2.22 (<.01)	1.91 (<.01)	1.90 (<.01)
No							
Placental ischemia and other hypoxia							
Yes	2.04 (<.01)		1.80 (<.01)	1.79 (<.01)	1.80 (<.01)	1.51 (<.01)	1.50 (<.01)
No							
Other biological determinants							
Yes	2.18 (<.01)		1.77 (<.01)	1.75 (<.01)	1.75 (<.01)	1.47 (<.01)	1.47 (<.01)
No							
Other pre-delivery covariates							
Other maternal medical conditions							
Yes	1.25 (<.01)			1.07 (.09)	1.06 (.15)	1.07 (.12)	1.07 (.10)
No							

	Univar. RR (p)	Block 1 RR (p)	Block 2 RR (p)	Block 3 RR (p)	Block 4 RR (p)	Block 5 RR (p)	Block 6 RR (p)
Labour variables							
Cord complications							
Yes	1.13 (<.01)				1.08 (.04)	1.10 (.01)	1.09 (.03)
No							
Forceps							
Yes	1.19 (.01)				1.07 (.28)		
No							
Vacuum extraction							
Yes	1.56 (<.01)				1.48 (.01)	1.58 (<.01)	1.54 (.01)
No							
Gestational age							
Gestational age							
Late preterm	8.09 (<.01)					6.21 (<.01)	6.14 (<.01)
Early term	1.58 (<.01)					1.55 (<.01)	1.54 (<.01)
Full term							
Other covariates							
Infant sex							
Male	1.37 (<.01)						1.31 (<.01)
Female							

* Block 6 is also the final model.

Table A.12. Model Building Steps for the Neonatal Respiratory Morbidity Multivariable Model (Chapter 3).

	Univar. RR (p)	Block 1 RR (p)	Block 2 RR (p)	Block 3 RR (p)	Block 4 RR (p)	Block 5 RR (p)	Block 6 RR (p)
Prenatal socio-demographic and lifestyle variables							
Maternal age							
<20 years	1.06 (.64)	0.77 (.05)	0.80 (.09)	0.80 (.09)	0.80 (.09)	0.85 (.20)	
20-34 years							
≥35 years	0.99 (.92)	1.07 (.34)	1.02 (.83)	1.01 (.85)	1.01 (.87)	0.99 (.88)	
Maternal marital status							
Single (never married)	1.36 (<.01)	1.26 (.01)	1.26 (<.01)	1.26 (<.01)	1.25 (.01)	1.19 (.02)	1.15 (.05)
Widowed, separated, divorced	0.85 (.55)	0.81 (.45)	0.79 (.39)	0.79 (.38)	0.79 (.39)	0.82 (.48)	0.82 (.46)
Common-law	1.21 (.01)	1.16 (.07)	1.15 (.06)	1.15 (.06)	1.15 (.07)	1.14 (.07)	1.14 (.07)
Married							
Median neighbourhood family income							
$50,000-$59,999	1.19 (.12)	1.11 (.37)					
$60,000-$69,999	1.08 (.50)	1.04 (.71)					
$70,000-$79,999	1.00 (.98)	0.97 (.81)					
$80,000-$89,999	0.88 (.32)	0.87 (.30)					
$90,000 or more							
Parity							
Nulliparous	1.20 (<.01)	1.30 (<.01)	1.22 (<.01)	1.22 (.01)	1.20 (<.01)	1.16 (.01)	1.12 (.03)
Primi/multiparous							
Previous preterm delivery							
Yes	1.66 (<.01)	1.83 (<.01)	1.72 (<.01)	1.71 (<.01)	1.70 (<.01)	1.12 (.24)	
No							
Previous abortion (spontaneous or induced)							
Yes	1.00 (.40)	0.97 (.64)					
No							

	Univar. RR (p)	Block 1 RR (p)	Block 2 RR (p)	Block 3 RR (p)	Block 4 RR (p)	Block 5 RR (p)	Block 6 RR (p)
Prenatal care							
None / inadequate	2.17 (<.01)	1.83 (<.01)	1.83 (<.01)	1.84 (<.01)	1.80 (<.01)	1.57 (.01)	1.54 (.01)
Normal / adequate							
Smoking during pregnancy							
Yes	1.14 (.05)	0.93 (.36)					
No							
Drug use during pregnancy							
Yes	1.90 (<.01)	1.63 (<.01)	1.49 (.01)	1.49 (.01)	1.51 (<.01)	1.30 (.06)	1.33 (.04)
No							
Alcohol during pregnancy							
Yes	1.05 (.81)	0.72 (.14)	0.69 (.09)	0.69 (.09)	0.70 (.09)	0.69 (.08)	0.68 (.07)
No							
Biological determinants of preterm birth							
Infection and inflammation							
Yes	1.79 (<.01)		1.76 (<.01)	1.75 (<.01)	1.77 (<.01)	1.51 (<.01)	1.50 (<.01)
No							
Placental ischemia and other hypoxia							
Yes	1.49 (<.01)		1.39 (<.01)	1.38 (<.01)	1.40 (<.01)	1.17 (.01)	1.16 (.01)
No							
Other biological determinants							
Yes	1.66 (<.01)		1.46 (<.01)	1.45 (<.01)	1.47 (<.01)	1.24 (.01)	1.25 (.01
No							
Other pre-delivery covariates							
Other maternal medical conditions							
Yes	1.16 (.01)			1.06 (.33)			
No							

	Univar. RR (p)	Block 1 RR (p)	Block 2 RR (p)	Block 3 RR (p)	Block 4 RR (p)	Block 5 RR (p)	Block 6 RR (p)
Labour variables							
Cord complications							
Yes	1.04 (.52)				1.03 (.61)		
No							
Forceps							
Yes	1.10 (.34)				1.01 (.92)		
No							
Vacuum extraction							
Yes	1.08 (.76)				1.10 (.71)		
No							
Gestational age							
Gestational age							
Late preterm	7.10 (<.01)					6.15 (<.01)	6.15 (<.01)
Early term	1.51 (<.01)					1.46 (<.01)	1.46 (<.01)
Full term							
Other covariates							
Infant sex							
Male	1.59 (<.01)						1.52 (<.01)
Female							

* Block 6 is also the final model.

Table A.13. Full Model for GEE Analysis of Mediation for NICU Triage/admission (Chapter 3).

	Adjusted β (95% CI)	Adjusted RR (95% CI)[1]
Intercept	-3.66 (-3.75, -3.57)	0.03 (0.02, 0.03)
Maternal age <20 years	-0.10 (-0.26, 0.07)	0.91 (0.77, 1.07)
Maternal age ≥35 years	0.12 (0.02, 0.21)	1.12 (1.02, 1.24)
Nulliparous	0.27 (0.20, 0.35)	1.31 (1.22, 1.42)
No / inadequate prenatal care	0.46 (0.27, 0.66)	1.59 (1.31, 1.93)
Smoking during pregnancy	0.07 (-0.03,0.16)	1.07 (0.97, 1.18)
Drug use during pregnancy	0.75 (0.60, 0.91)	2.12 (1.82, 2.48)
Infection and inflammation	0.64 (0.55, 0.74)	1.90 (1.72, 2.09)
Placental ischemia and other hypoxia	0.41 (0.33, 0.49)	1.50 (1.39, 1.62)
Other biological determinants	0.38 (0.28, 0.49)	1.47 (1.33, 1.62)
Other maternal medical conditions	0.07 (-0.01, 0.16)	1.08 (0.99, 1.17)
Cord complications	0.08 (0.01, 0.16)	1.09 (1.01, 1.17)
Vacuum extraction	0.43 (0.13, 0.73)	1.54 (1.14, 2.07)
Male sex	0.27 (0.20, 0.34)	1.31 (1.22, 1.41)
G	0.22 (0.18, 0.26)	1.25 (1.20, 1.30)
G*Maternal age <20 years	-0.06 (-0.11, 0.00)	0.95 (0.90, 1.00)
G*Maternal age ≥35 years	0.03 (0.00, 0.06)	1.03 (1.00, 1.06)
G*Nulliparous	-0.01 (-0.03, 0.02)	0.99 (0.97, 1.02)
G*No / inadequate prenatal care	0.19 (0.10, 0.30)	1.22 (1.10, 1.34)
G*Smoking during pregnancy	0.05 (0.02, 0.08)	1.06 (1.02, 1.09)
G*Drug use during pregnancy	0.14 (-0.06, 0.21)	1.15 (1.07, 1.23)
G*Infection and inflammation	0.15 (0.10, 0.19)	1.16 (1.11, 1.21)
G*Placental ischemia and other hypoxia	0.18 (0.15, 0.21)	1.19 (1.16, 1.23)
G*Other biological determinants	0.19 (0.15, 0.23)	1.21 (1.16, 1.26)
G*Other maternal medical conditions	0.01 (-0.02, 0.03)	1.01 (0.98, 1.03)
G*Cord complications	-0.01 (-0.04, 0.01)	0.99 (0.96, 1.01)
G*Vacuum extraction	-0.07 (-0.18, 0.03)	0.93 (0.84, 1.03)
G*Male sex	0.04 (0.02, 0.06)	1.04 (1.02, 1.06)
Mstar2	1.82 (1.72 (1.90)	6.14 (5.63, 6.71)
Mstar1	0.43 (0.35, 0.52)	1.54 (1.41, 1.71)

* Only the level of the dummy variable under analysis is shown.

[1] Note: G*variable interactions match indirect effect of covariates through gestational age.

Table A.14. Full Model for GEE Analysis of Mediation for Neonatal Respiratory Morbidity (Chapter 3).

	Adjusted β (95% CI)	Adjusted RR (95% CI)[1]
Intercept	-4.10 (-4.22, -3.99)	0.02 (0.01, 0.02)
Single (never married)	0.13 (-0.01, 0.27)	1.14 (0.99, 1.31)
Divorced, separated, widowed	-0.20 (-0.74, 0.34)	0.82 (0.48, 1.40)
Common law	0.14 (0.00, 0.29)	1.15 (1.00, 1.33)
Nulliparous	0.12 (0.01, 0.22)	1.12 (1.01, 1.25)
No / inadequate prenatal care	0.43 (0.11, 0.75)	1.54 (1.12, 2.12)
Drug use during pregnancy	0.28 (0.01, 0.55)	1.33 (1.01, 1.74)
Alcohol use during pregnancy	-0.38 (-0.80, 0.04)	0.68 (0.45, 1.04)
Infection and inflammation	0.41 (0.25, 0.56)	1.50 (1.29, 1.75)
Placental ischemia and other hypoxia	0.15 (0.04, 0.27)	1.16 (1.04, 1.31)
Other biological determinants	0.23 (0.07, 0.39)	1.25 (1.07, 1.47)
Male sex	0.42 (0.31, 0.52)	1.52 (1.36, 1.69)
G	0.21 (0.16, 0.25)	1.23 (1.17, 1.29)
G*Single (never married)	0.05 (0.02, 0.08)	1.06 (1.02, 1.09)
G*Divorced, separated, widowed	-0.01 (-0.10, 0.08)	1.00 (0.92, 1.10)
G*Common law	0.01 (-0.01, 0.04)	1.01 (0.99, 1.04)
G*Nulliparous	-0.02 (-0.04, 0.00)	0.98 (0.96, 1.00)
G*No / inadequate prenatal care	0.14 (0.05, 0.23)	1.15 (1.06, 1.26)
G*Drug use during pregnancy	0.14 (0.07, 0.21)	1.15 (1.07, 1.24)
G*Alcohol use during pregnancy	0.00 (-0.09, 0.09)	1.00 (0.92, 1.10)
G*Infection and inflammation	0.15 (0.11, 0.20)	1.17 (1.12, 1.22)
G*Placental ischemia and other hypoxia	0.19 (0.16, 0.22)	1.21 (1.17, 1.25)
G*Other biological determinants	0.18 (0.14, 0.22)	1.20 (1.15, 1.25)
G*Male sex	0.03 (0.02, 0.05)	1.03 (1.02, 1.05)
Mstar2	1.82 (1.69, 1.95)	6.16 (5.39, 7.03)
Mstar1	0.38 (0.25, 0.50)	1.46 (1.29, 1.65)

* Only the level of the dummy variable under analysis is shown.

[1] Note: G*variable interactions match indirect effect of covariates through gestational age.

Table A.15. NICU Triage/admission Multivariable Model with Labour Pathway Variables Added (Chapter 3).

	% triaged / admitted	Unadjusted RR (95% CI)	Adjusted RR (95% CI)
Prenatal socio-demographic and lifestyle variables			
Maternal age			
<20 years	8.0	1.20 (1.02, 1.40)	0.97 (0.82, 1.14)
20-34 years	6.7	reference	reference
≥35 years	7.5	1.13 (1.02, 1.24)	1.09 (0.99, 1.20)
Maternal marital status			
Single (never married)	8.8	1.38 (1.25, 1.52)	---
Widowed, separated, divorced	7.7	1.21 (0.86, 1.69)	
Common-law	7.2	1.12 (1.01, 1.25)	---
Married	6.4	reference	
Median neighbourhood family income			
$50,000-$59,999	7.6	1.14 (0.97, 1.33)	---
$60,000-$69,999	6.9	1.03 (0.88, 1.21)	
$70,000-$79,999	6.5	0.98 (0.82, 1.16)	
$80,000-$89,999	6.1	0.91 (0.76, 1.08)	
$90,000 or more	6.7	reference	
Parity			
Nulliparous	8.1	1.39 (1.29, 1.50)	1.22 (1.13, 1.32)
Primi/multiparous	5.9	reference	reference
Previous preterm delivery			
Yes	9.7	1.45 (1.27, 1.67)	---
No	6.7	reference	
Previous abortion (induced, spontaneous)			
Yes	7.0	1.02 (0.94, 1.10)	---
No	6.8	reference	
Prenatal care			
None / inadequate	19.2	2.87 (2.40, 3.43)	1.53 (1.23, 1.88)
Normal / adequate	6.7	reference	reference
Smoking during pregnancy			
Yes	9.1	1.42(1.30, 1.55)	1.07 (0.98, 1.18)
No	6.4	reference	reference
Drug use during pregnancy			
Yes	22.0	3.40 (2.99, 3.86)	2.12 (1.80, 2.50)
No	6.5	reference	reference
Alcohol during pregnancy			
Yes	11.4	1.68 (1.35, 2.10)	---
No	6.8	reference	

	% triaged / admitted	Unadjusted RR (95% CI)	Adjusted RR (95% CI)
Biological determinants of preterm birth			
Infection and inflammation			
Yes	16.1	2.62 (2.39, 2.88)	1.70 (1.54, 1.87)
No	6.1	reference	reference
Placental ischemia and other hypoxia			
Yes	11.5	2.02 (1.87, 2.19)	1.43 (1.32, 1.55)
No	5.7	reference	reference
Other biological determinants			
Yes	12.7	1.99 (1.80, 2.21)	1.32 (1.19, 1.47)
No	6.4	reference	reference
Other pre-delivery covariates			
Other maternal medical conditions			
Yes	8.1	1.25 (1.15, 1.36)	1.04 (0.96, 1.13)
No	6.5	reference	reference
Labour variables			
Cord complications			
Yes	7.5	1.13 (1.04, 1.22)	1.05 (0.97, 1.13)
No	6.6	reference	reference
Forceps			
Yes	8.0	1.19 (1.04, 1.35)	---
No	6.8	reference	
Vacuum extraction			
Yes	10.7	1.56 (1.17, 2.08)	1.38 (1.02, 1.87)
No	6.8	reference	reference
Non-reassuring fetal heart rate			
Yes	13.1	2.28 (2.11, 2.46)	2.00 (1.84, 2.17)
No	5.7	reference	reference
Fetal distress			
Yes	20.5	3.11 (2.70, 3.60)	1.36 (1.16, 1.60)
No	6.6	reference	reference
Labour onset			
No labour	10.7	1.78 (1.59, 1.99)	1.57 (1.40, 1.77)
Induced labour	7.3	1.21 (1.12, 1.31)	1.02 (0.94, 1.11)
Spontaneous labour	6.0	reference	reference
Gestational age			
Gestational age			
Late preterm	38.9	8.09 (7.46, 8.77)	6.13 (5.60, 6.71)
Early term	7.7	1.68 (1.54, 1.84)	1.54 (1.41, 1.68)
Full term	4.6	reference	reference
Other covariates			
Infant sex			
Male	7.9	1.37 (1.27, 1.48)	1.30 (1.21, 1.40)
Female	5.8	reference	reference

--- : p>.20 in final model.

Table A.16. Neonatal Respiratory Morbidity Multivariable Model with Labour Pathway Variables Added (Chapter 3).

	% with resp morb	Unadjusted RR (95% CI)	Adjusted RR (95% CI)
Prenatal socio-demographic and lifestyle variables			
Maternal age			
<20 years	3.7	1.06 (0.84, 1.34)	---
20-34 years	3.5	reference	
≥35 years	3.5	0.99 (0.86, 1.14)	
Maternal marital status			
Single (never married)	4.4	1.36 (1.18, 1.56)	1.21 (1.04, 1.39)
Widowed, separated, divorced	2.8	0.85 (0.49, 1.46)	0.79 (0.47, 1.35)
Common-law	4.0	1.21 (1.05, 1.39)	1.16 (1.01, 1.34)
Married	3.3	reference	reference
Median neighbourhood family income			
$50,000-$59,999	4.0	1.20 (0.95, 1.51)	---
$60,000-$69,999	3.6	1.08 (0.86, 1.35)	
$70,000-$79,999	3.3	1.00 (0.78, 1.29)	
$80,000-$89,999	2.9	0.88 (0.68, 1.13)	
$90,000 or more	3.3	reference	
Parity			
Nulliparous	3.9	1.20 (1.08, 1.33)	1.09 (0.98, 1.21)
Primi/multiparous	3.2	reference	reference
Previous preterm delivery			
Yes	5.6	1.66 (1.38,1.99)	---
No	3.4	reference	
Previous abortion (induced, spontaneous)			
Yes	3.5	1.00 (0.89, 1.12)	---
No	3.5	reference	
Prenatal care			
None / inadequate	7.5	2.17 (1.62, 2.91)	1.46 (1.05, 2.04)
Normal / adequate	3.5	reference	reference
Smoking during pregnancy			
Yes	3.9	1.14 (1.00, 1.31)	---
No	3.4	reference	
Drug use during pregnancy			
Yes	6.5	1.90 (1.48, 2.43)	1.31 (1.00, 1.73)
No	3.5	reference	reference
Alcohol during pregnancy			
Yes	3.7	1.05 (0.70, 1.57)	0.70 (0.46, 1.06)
No	3.5	reference	reference

	% with resp morb	Unadjusted RR (95% CI)	Adjusted RR (95% CI)
Biological determinants of preterm birth			
Infection and inflammation			
Yes	6.3	1.90 (1.63, 2.22)	1.39 (1.19, 1.62)
No	3.3	reference	reference
Placental ischemia and other hypoxia			
Yes	4.7	1.48 (1.31, 1.66)	1.12 (1.00, 1.27)
No	3.2	reference	reference
Other biological determinants			
Yes	5.3	1.56 (1.33, 1.83)	1.17 (0.99, 1.38)
No	3.4	reference	reference
Other pre-delivery covariates			
Other maternal medical conditions			
Yes	3.9	1.16 (1.03, 1.31)	---
No	3.4	reference	
Labour variables			
Cord complications			
Yes	3.6	1.04 (0.93, 1.16)	---
No	3.5	reference	
Forceps			
Yes	3.8	1.10 (0.91, 1.33)	---
No	3.5	reference	
Vacuum extraction			
Yes	3.8	1.08 (0.66, 1.78)	---
No	3.5	reference	
Non-reassuring fetal heart rate			
Yes	5.8	1.88 (1.67, 2.12)	1.87 (1.65, 2.12)
No	3.1	reference	reference
Fetal distress			
Yes	8.1	2.36 (1.86, 3.00)	1.21 (0.94, 1.56)
No	3.4	reference	reference
Labour onset			
No labour	6.1	1.81 (1.55, 2.11)	1.75 (1.50, 2.05)
Induced labour	3.2	0.95 (0.85, 1.07)	0.89 (0.79, 1.01)
Spontaneous labour	3.4	reference	reference
Gestational age			
Gestational age			
Late preterm	17.7	7.10 (6.27, 8.05)	5.97 (5.22, 6.84)
Early term	3.8	1.51 (1.33, 1.71)	1.41 (1.24, 1.60)
Full term	2.5	reference	reference
Other covariates			
Infant sex			
Male	4.3	1.59 (1.43, 1.77)	1.51 (1.36, 1.68)
Female	2.7	reference	reference

--- : p>.20 in final model.

A.8 Additional Analyses for Chapter 5

A.8.1 Regression Diagnostics

Regression diagnostics were performed to test for outliers and influential observations in the final multivariable models. Because regression diagnostic procedures have not been developed for multinomial logistic regression, Hosmer and Lemeshow (58) recommend assessing the fit of two logistic regression models (one for each testable level of the polytomous outcome) and then integrating the results. (See A.7.1 for details.)

Results for the DFbetas are in Table A.17. The C statistic from <0.01 to 0.17 (late preterm vs. full term) and from <0.01 to 0.03 (early term vs. full term). Because no values were influential, no observations were deleted from the analysis.

A.8.2 Model Building Steps

The steps used to perform blockwise model building (as described in Appendix A.4.2) are shown in Table A.18.

Table A.17. DFbetas for Final Spontaneous Late Preterm or Early Term Birth Multivariable Model (Chapter 5).

	Late preterm vs. full term		Early term vs. full term	
	Range	No. >2	Range	No. >2
Young maternal age	-0.05, 0.16	0	-0.04, 0.07	0
Old maternal age	-0.07, 0.09	0	-0.03, 0.04	0
Single	-0.05, 0.09	0	-0.03, 0.04	0
Divorced, separated, widowed	-0.11, 0.35	0	-0.09, 0.13	0
Common law	-0.07, 0.11	0	-0.05, 0.05	0
$50,000-$59,999	-0.15, 0.06	0	-0.06, 0.03	0
$60,000-$69,999	-0.15, 0.06	0	-0.06, 0.04	0
$70,000-$79,999	-0.14, 0.06	0	-0.05, 0.04	0
$80,000-$89,999	-0.14, 0.06	0	-0.05, 0.04	0
Nulliparous	-0.08, 0.05	0	-0.03, 0.03	0
Previous preterm delivery	-0.07, 0.08	0	-0.05, 0.05	0
No or inadequate prenatal care	-0.12, 0.20	0	-0.09, 0.12	0
Drug use during pregnancy	-0.11, 0.18	0	-0.08, 0.10	0
Infection and inflammation	-0.08, 0.11	0	-0.04, 0.07	0
Placental ischemia and other hypoxia	-0.05, 0.07	0	-0.03, 0.04	0
Other biological determinants	-0.09, 0.12	0	-0.06, 0.06	0
Maternal medical conditions	-0.05, 0.07	0	-0.03, 0.03	0
Major or minor congenital anomalies	-0.12, 0.15	0	-0.06, 0.07	0
Male fetal sex	-0.05, 0.04	0	-0.02, 0.02	0

* Only the level of the dummy variable under analysis is shown.

Table A.18. Model Building Steps for Spontaneous Late Preterm and Early Term Birth Multivariable Model (Chapter 5).

	Univar. RR (p)		Block 1 RR (p)		Block 2 RR (p)		Block 3 RR (p)	
	LPT	ET	LPT	ET	LPT	ET	LPT	ET
Prenatal socio-demographic and lifestyle variables								
Maternal age								
<20 years	1.08 (.62)	1.01 (.90)	0.69 (.03)	1.04 (.67)	0.74 (.08)	1.08 (.43)	0.75 (.08)	1.08 (.41)
20-34 years								
≥35 years	1.17 (.08)	1.02 (.74)	1.38(<.01)	1.00 (.95)	1.28 (.01)	0.97 (.55)	1.27 (.02)	0.97 (.51)
Maternal marital status								
Single (never married)	1.58 (<.01)	1.01 (.90)	1.25 (.05)	0.96 (.49)	1.30 (.02)	0.98 (.80)	1.30 (.02)	0.98 (.78)
Widowed, separated, divorced	1.02 (<.01)	1.01 (.90)	1.08 (.45)	0.91 (.09)	0.93 (.84)	1.25 (.19)	0.92 (.82)	1.25 (.19)
Common-law	1.28 (.01)	0.95 (.28)	0.90 (.77)	1.21 (.26)	1.11 (.30)	0.93 (.16)	1.12 (.29)	0.93 (.17)
Married								
Median neighbourhood family income								
$50,000-$59,999	1.51 (.01)	1.06 (.50)	1.34 (.10)	1.06 (.51)	1.37 (.09)	1.06 (.52)	1.35 (.10)	1.06 (.50)
$60,000-$69,999	1.46 (.02)	1.04 (.90)	1.25 (.05)	0.96 (.49)	1.30 (.02)	0.98 (.80)	1.30 (.02)	0.98 (.78)
$70,000-$79,999	1.02 (.95)	1.27 (.13)	1.08 (.45)	0.91 (.09)	0.93 (.84)	1.25 (.19)	0.92 (.82)	1.25 (.19)
$80,000-$89,999	1.11 (.55)	1.00 (.99)	1.16 (.45)	1.02 (.84)	1.18 (.40)	1.02 (.81)	1.15 (.48)	1.03 (.78)
$90,000 or more								
Parity								
Nulliparous	1.22 (<.01)	0.83 (<.01)	2.01 (<.01)	0.92(.05)	1.85(<.01)	0.91(.03)	1.82(<.01)	0.91(.03)
Primi/multiparous								

	Univar. RR (p)		Block 1 RR (p)		Block 2 RR (p)		Block 3 RR (p)	
	LPT	ET	LPT	ET	LPT	ET	LPT	ET
Previous preterm delivery								
Yes	6.55 (<.01)	2.58 (<.01)	9.06 (<.01)	2.49 (<.01)	8.52 (<.01)	2.43 (<.01)	8.46 (<.01)	2.43 (<.01)
No								
Previous abortion (spontaneous or induced)								
Yes	1.11 (.16)	1.04 (.32)	1.00 (.96)	1.01 (.89)				
No								
Prenatal care								
None / inadequate	3.87 (<.01)	1.55 (<.01)	2.78 (<.01)	1.44 (.02)	2.78 (<.01)	1.47 (.01)	2.77 (<.01)	1.47 (.01)
Normal / adequate								
Smoking during pregnancy								
Yes	1.53 (<.01)	1.11 (.03)	1.15 (.19)	1.05 (.42)				
No								
Drug use during pregnancy								
Yes	2.94 (<.01)	1.46 (<.01)	1.84 (<.01)	1.17 (.23)	1.77 (<.01)	1.23 (.12)	1.77 (<.01)	1.22 (.12)
No								
Alcohol during pregnancy								
Yes	1.62 (.03)	1.27 (.07)	1.01 (.97)	1.17 (.30)				
No								
Biological determinants of preterm birth								
Infection and inflammation								
Yes	2.34 (<.01)	0.90 (.19)			2.10 (<.01)	0.88 (.13)	2.07 (<.01)	0.88 (.13)
No								

	Univar. RR (p)		Block 1 RR (p)		Block 2 RR (p)		Block 3 RR (p)	
	LPT	ET	LPT	ET	LPT	ET	LPT	ET
Placental ischemia and other hypoxia								
Yes	2.43 (<.01)	1.33 (<.01)			2.28 (<.01)	1.27 (<.01)	2.21 (<.01)	1.25 (<.01)
No								
Other biological determinants								
Yes	4.17 (<.01)	2.63 (<.01)			3.71 (<.01)	2.54 (<.01)	3.61 (<.01)	2.52 (<.01)
No								
Other pre-delivery covariates								
Other maternal medical conditions								
Yes	1.47 (<.01)	1.13 (.01)					1.30 (<.01)	1.20 (.04)
No								
Fetal anomalies								
Yes	1.50 (.01)	1.23 (.02)					1.35 (.06)	1.20 (.04)
No								
Fetal sex								
Male	1.38 (<.01)	1.08 (.04)					1.35 (<.01)	1.05 (.25)
Female								

* Block 3 is also the final model.

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Appendix B

Objective Two Details

B.1 Data Source Details

B.1.1 National Longitudinal Survey of Children and Youth

The National Longitudinal Survey of Children and Youth (**NLSCY**) was conducted by Statistics Canada and Human Resources Development Canada from 1994/1995 to 2008/2009. The overall purpose of the NLSCY was to obtain information on indicators of children's physical, emotional, behavioural, and social development (1).

The NLSCY is a probability survey (1). Children were identified through the Labour Forces Survey, a monthly panel survey that collects market data from a national sample of over 52,000 dwellings in rotation groups that change monthly to maintain representativeness and minimize respondent burden. The Labour Forces Survey is based on a stratified, multistage design that uses probability sampling at each stage of the design. Primary strata are defined by the intersection of Economic Regions and Employment Insurance Economic Regions and are classified as urban, rural, or remote. Secondary strata are defined by population density and income. Each stratum is then divided into clusters (i.e., city blocks, apartment buildings, towns, or enumeration areas, depending on population density). A sample of clusters is selected, and dwellings are sampled systematically from the selected clusters based on a pre-defined list that depends on the type of strata and, for urban areas, the size of the city. The sample for the NLSCY was allocated so that there was a sufficient sample size to produce reliable estimates in each age group at the national level and in 0 to 11 year olds at the provincial level.

Data were collected by computer-assisted telephone interviewing (**CATI**) or computer-assisted personal interviewing (**CAPI**) in which the interviewer reads questions on the computer and enters the respondent's answers. The use of computers allows complex flows and edits to be built into the survey, thus increasing efficiency and accuracy in the interview process (1).

The survey consists of (relevant to this thesis) a Household Component, an Adult Component, and a Child Component (1). The Household Component collects information on relationships among household members, contact information, and demographic

characteristics (e.g., sex, birthdate). The person most knowledgeable (**PMK**) about the child is identified during this interview. This individual then becomes the respondent for subsequent stages of the survey. The Adult Component collects information on the PMK and his or her partner. The Child Component collects information on the child. For children aged 0 to 17 years, the PMK is the respondent even for the Child Component. There are also direct assessments of the child, including the Peabody Picture Vocabulary Test-Revised, which require in-person testing.

A number of procedures were undertaken to ensure high quality data collection. Interviewers were trained using classroom teaching and self-study materials. Senior interviewers dealt with refusal and non-response. Interviewers were able to complete surveys in English or French, and if the respondent required another language, effort was made to identify an interviewer who spoke the language. Very few interviews were incomplete because of language barriers (e.g., N=80 in Cycle 8) (1).

B.1.2 Early Childhood Development Cohorts

The NLSCY consists of an Original Cohort (followed from Cycle 1 [0 to 11 years of age] to Cycle 8 [14 to 25 years of age]) and several Early Childhood Development (**ECD**) Cohorts which were recruited at 0 to 1 years of age in Cycles 2 through 8 and followed for one to four cycles (depending on when they were recruited). See Figure B.1 and Table B.1 for an illustration of the study design and the sample sizes in a given ECD Cohort.

ECD Cohorts can be examined cross-sectionally or longitudinally. Their purpose was to collect detailed information on indicators relevant to young children, such as language skills, motor and social development, and behaviour. Like the Original Cohort, children in the ECD Cohorts were sampled from the Labour Forces Survey.

B.1.3 Pooling Early Childhood Development Cohorts

To accrue a large enough sample size for the current study, 0 to 1 year olds in the ECD Cohorts of Cycles 2 through 6 were pooled and followed forward for two subsequent cycles (i.e., to Cycles 4 through 8). Pooling of ECD Cohorts can be undertaken when the sample size in individual cohorts is too small, and has been undertaken previously (2).

However, several assumptions must be made. These assumptions, and their applicability to this thesis, are discussed below.

1. *Across cycles, each survey sample must be considered to represent the same population* (3). For each ECD Cohort, the sample can be said to represent children of the same age living in Canada at the time of data collection. It is therefore reasonable to assume that the population of interest is the same across the study period (i.e., 1996/1997-2004/2005) even though social conditions have changed over time. Therefore, the reference group for Chapter 4 is all 0 to 1 year olds who were born during the years covered by the pooled cycles. Note that it is possible that the gestational age distribution may have changed across time, given changes in clinical practice (4). We tested this assumption, and the results can be seen in Table B.2. Although there were small changes in the gestational age distribution across cycles, these were taken into account by controlling for cycle of entry into the NLSCY in the analysis.

2. *Survey designs must be the same across cycles* (3). Changes across time to the ECD design are summarized in Table B.3. It is expected that these changes did not affect our analyses for the following reasons: Because the 2004 Labour Forces Survey redesign aimed to reflect changes in the Canadian population, the redesign aided in maintaining the same target population. Although twins were sampled in Cycles 2 through 4 but not later, multiple gestations were excluded from our study. Likewise, although 0 to 5 year olds (not 0 to 1 year olds) were sampled in Cycle 6, only 0 to 1 year olds were included in our study. Finally, while there were changes across time in how non-respondents were treated, our study sample only included children with data at each cycle of data collection, and the NLSCY offers funnel weights for later cycles which are equivalent to longitudinal weights used in previous cycles when a child could not enter and exit the cohort.

3. *Questionnaires and mode of delivery should be the same across cycles* (3). For all cycles, interviews were completed via telephone using CATI for 0 to 3 year olds and in person using CAPI for older children. There were minimal changes to the

questionnaires for questions included in the current study. (See Table B.3.) The effect of these changes is expected to be negligible.

4. *The type of respondent should be the same across cycles* (3). We restricted our study sample to children whose respondent was the biological mother at all stages of follow-up. This enabled us to be sure that questions regarding pregnancy would be accurate and complete, and also addresses the issue of uniformity of type of respondent across cycles. The effect of this decision on the sample size is shown in Table B.4.

5. *Samples should be independent across cycles* (3). If a researcher were interested in outcomes for 0 to 3 year olds and pooled several cycles, 0 to 1 year olds in the first cycle would be 2 to 3 year olds in the second cycle and so would be counted twice. This is not an issue for this thesis since we treated our sample as a longitudinal sample. For example, although individuals who were 0 to 1 year olds in the first cycle were included as 2 to 3 year olds in the second cycle, the outcome was only assessed in 2 to 3 year olds, and data collected at 0 to 1 years was considered to be previous data collection on the same individuals.

Figure B.1. NLSCY Cycles of Data Collection (Adapted from Statistics Canada, 2009).

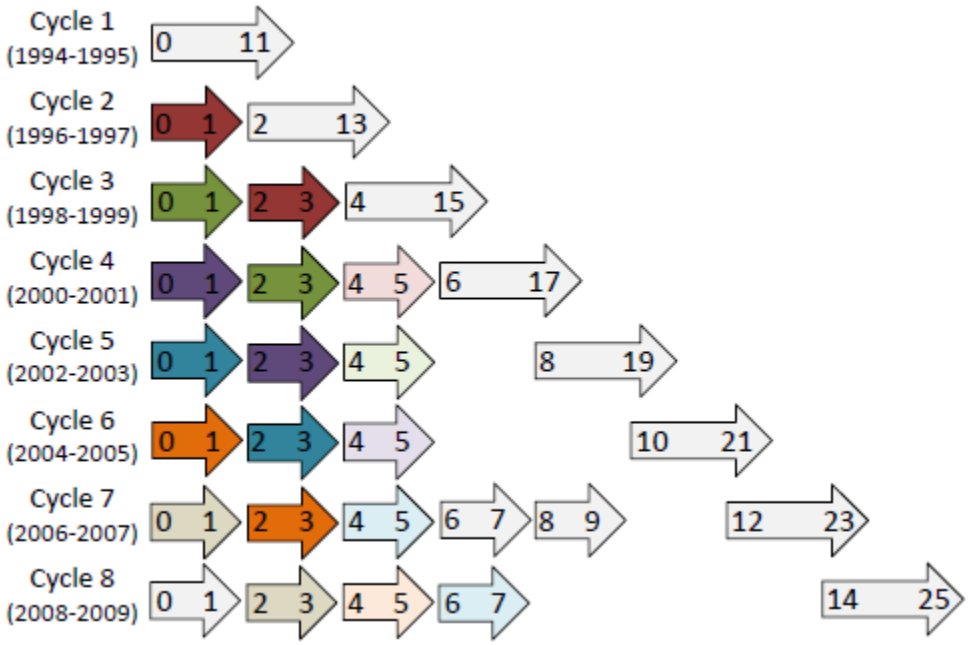

Table B.1. Sample Sizes across Early Childhood Development Cycles.

Cycle of entry	Age of child and number of respondents at Cycle						
	Cycle 2	Cycle 3	Cycle 4	Cycle 5	Cycle 6	Cycle 7	Cycle 8
Cycle 2	0-1 years 3,560	2-3 years 2,994	4-5 years 2,103				
Cycle 3		0-1 years 6,995	2-3 years 5,741	4-5 years 4,815			
Cycle 4			0-1 years 2,432	2-3 years 1,808	4-5 years 1,486		
Cycle 5				0-1 years 2,593	2-3 years 2,065	4-5 years 1,799	
Cycle 6					0-1 years 2,951	2-3 years 2,491	4-5 years 2,099

Table B.2. Changes in the Gestational Age Distribution across Cycles of the NLSCY (N=18,531).

	Late preterm N (%)	Early term N (%)	Full term N (%)
Cycle 2	163.8 (7.4)	1,001.3 (28.1)	2,295.0 (64.5)
Cycle 3	448.6 (6.4)	1,998.2 (28.6)	4,548.2 (65.0)
Cycle 4	208.9 (8.6)	680.4 (28.0)	1,542.7 (63.4)
Cycle 5	183.8 (7.1)	750.4 (28.9)	1,658.8 (63.4)
Cycle 6	239.5 (8.1)	915.5 (31.0)	1,796.0 (60.9)

* Chi square test for trend: p=.01 late preterm vs. full term; p=.02 early term vs. full term.

Table B.3. Summary of Changes to the Early Childhood Development Cohorts Design and Questionnaire across Time.

Component	Description of original	Description of change
Design		
Source of participants	The Labour Forces Survey is redesigned every 10 years. Cycles 2 through 5 are covered by the 1994 redesign.	Cycles 6 through 8 are covered by the 2004 redesign.
Number of children sampled per household	In the NLSCY, only 1 child per household in sampled. In Cycles 2 through 4, an exception is twins.	In Cycles 5 through 8, only one child per household was sampled (including twins).
Ages of children sampled	In Cycles 2 through 5, 0-1 year olds were sampled.	In Cycle 6, 0-5 year olds were sampled.
Treatment of non-respondents	In Cycles 2 through 6, children were only surveyed if they responded to the previous cycle.	In Cycles 7 and 8, all children were surveyed, even if they did not respond to the previous cycle.
Questionnaire		
Neonatal health	Cycles 2 through 5: “In general, would you say this child’s health at birth was: …”	Cycle 6, 7: "Compared to other babies in general…"
Parenting	Scales include parenting interactions, parenting effectiveness, parenting consistency, rational parenting subscales	Cycle 4 also has “conflict resolution” scale.

Table B.4. Proportion of the Study Sample per Cycle that was Excluded for Having a Respondent other than the Biological Mother.

Cycle of entry	0-1 years N (%)	2-3 years N (%)	4-5 years N (%)
Cycle 2	338.7 (1.6)	163.6 (1.0)	137.0 (1.1)
Cycle 3	558.1 (2.7)	462.3 (2.8)	247.4 (1.9)
Cycle 4	468.5 (2.3)	332.0 (2.0)	142.9 (1.1)
Cycle 5	483.0 (2.3)	234.1 (1.4)	79.8 (0.6)
Cycle 6	349.7 (1.7)	134.1 (0.8)	98.8 (0.8)
TOTAL6	2,198.0 (10.6)	1,326.1 (8.0)	705.9 (5.5)

B.2 Variable Selection and Measurement

Table B.5 shows evidence for the relationship between each variable and poor developmental outcomes as well as a description of potential measurement issues, where applicable. Table B.6 describes each variable as it was measured in the data source as well as its format for analysis. Table B.7 includes the NLSCY questionnaire items for the scales which measured maternal mental health, family functioning, parenting interactions, parenting effectiveness, parenting consistency, and child motor and social development at 2 to 3 years of age.

Table B.5. Justification of Inclusion of Variables and Potential Measurement Issues for Chapter 4.

Variable	Association with poor developmental outcomes	Potential measurement issues
Perinatal variables		
Smoking during pregnancy	There is a small but important association between smoking during pregnancy and poor developmental outcomes (5).	Self-report of smoking during pregnancy underestimates the true prevalence in comparison to cotinine samples (6, 7).
Alcohol use during pregnancy	Alcohol use is predictive of poor development; this is likely due to excessive (not minimal) consumption (8).	Self-report of alcohol use during pregnancy underestimates the true prevalence (9).
Placental ischemia and other hypoxia	Gestational hypertension and preeclampsia are associated with increased risk for low IQ (10, 11).	There tends to be high sensitivity and specificity for common conditions (hypertension) but not rare conditions (abruption) (12).
Other biological determinants	Children born to mothers with gestational diabetes are at increased risk for low IQ and motor delays (13).	There tends to be higher specificity than sensitivity in recall of gestational diabetes (7, 12).
Delivery mode	Caesarean section is a marker of indications associated with poor outcomes (10, 11, 13).	Maternal recall of delivery by caesarean section is highly accurate (9, 12).
Gestational age		
Gestational age	See literature review.	Maternal recall of gestational age is valid but imprecise. The most common error is misclassification within 1 week (6, 14).
Infant and neonatal variables		
Neonatal special care	NICU admission and resuscitation are associated with developmental delay and low IQ (15, 16).	There is high agreement between maternal recall and antenatal records of neonatal special care and transfers but lower agreement for complications (9, 17).
Breastfeeding	Failure to breastfeed is associated with poor health and cognitive development (18, 19).	

Variable	Association with poor developmental outcomes	Potential measurement issues
Social context: family structure		
Maternal partnership status	Single parent status as well as transitions into and out of relationships have a negative impact on development (20, 21)	
Number of siblings	Larger family size is associated with poor academic performance (22).	
Social context: family resources		
Family income adequacy	Financial strain is linked with child developmental disability (23).	
Current maternal education	Maternal education is a strong predictor of child development and reflects a mother's psychological capital (24, 25).	
Maternal age (at birth of child)	Young maternal age is associated with poor child development but this is likely explained by socioeconomic factors (26).	
Maternal health	Poor maternal health, especially chronic disease, is related to child development and academic performance (27).	
Maternal mental health	Poor maternal mental health is associated with poor school readiness and cognitive and motor delays (28, 29).	Cronbach's alphas for mental health measurement in the NLSCY are 0.82 (0-1 years), 0.80 (2-3 years), 0.82 (4-5 years) (1).
Social context: other		
Family functioning	Poor family functioning is associated with developmental delay (30).	Cronbach's alphas for family functioning measurement in the NLSCY are 0.91 (0-1 years), 0.91 (2-3 years), 0.92 (4-5 years) (1).
Proximal social processes		
Parenting interactions	Negative interactions and harsh discipline are associated with child behaviour problems (31).	Cronbach's alpha in the NLSCY is 0.68 across ages groups. There may be social desirability (32).

Variable	Association with poor developmental outcomes	Potential measurement issues
Parenting effectiveness	Negative interactions and harsh discipline are associated with child behaviour problems (31).	Cronbach's alphas in the NLSCY range from 0.61 to 0.63 across ages groups. There may be social desirability (32).
Parenting consistency	Negative interactions and harsh discipline are associated with child behaviour problems (31).	Cronbach's alphas in the NLSCY range from 0.67 to 0.72 across ages groups. There may be social desirability (32).
Other covariates		
Child sex	Boys are more vulnerable than girls to developmental delay and poor academic performance (33).	
Developmental outcomes		
Developmental delay	n/a	Maternal report of child outcomes may be distorted by the mother's own health or socioeconomic status (28, 29, 31, 34).
Receptive vocabulary delay	n/a	

Table B.6. Description of Variables Included in Chapter 4 Analyses.

Variable	Description	Scale of measurement	
		Original	Analysis
Perinatal variables			
Smoking during pregnancy	Any smoking by mother during pregnancy	Yes; No	Yes; No
Alcohol use during pregnancy	Frequency of alcohol use by mother during pregnancy	Every day; 4-6 / week; 2-3 / week; once / week; Never	Ever; Never
Placental ischemia and other hypoxia	High blood pressure during pregnancy with child; small birth weight for gestational age ($<5^{th}$ percentile)	n/a (Derived)	Yes (1 or more); No
Other biological determinants	Diabetes during pregnancy with child	n/a (Derived)	Yes (1 or more); No
Delivery mode	Vaginal or caesarean delivery	Caesarean; Vaginal	Caesarean; Vaginal
Gestational age			
Gestational age	Days before or after the due date the child was born	Continuous (days)	Late preterm; Early term; Full term
Infant and neonatal factors			
Neonatal special care	If used special medical care, intensive care; ventilation or oxygen; or transfer to a specialized hospital	n/a (Derived)	Yes (1 or more); No
Breastfeeding	If breastfed at all, length of breastfeeding	<1, 1-4, 5-8, or 3-12 weeks; 3-6, 7-9, 10-12, 13-16, or >16 months; current	≤6 months; 7-12 months; never

Variable	Description	Scale of measurement	
		Original	Analysis
Social context: family structure			
Maternal partnership status	Maternal status (at each time point)	Single; Divorced; Widowed; Common law; Married	Consistently single parent; Any transition; Consistently two-parent
Number of siblings	Total number of siblings living in household at time of interview (including full, half, step, adopted, and foster siblings)	Continuous (number)	≥3 siblings; 1-2 siblings; no siblings
Social context: family resources			
Family income adequacy	Derived by Statistics Canada based on household income and household size (1-2 persons, 3-4 persons, or 5 or more persons)	Lowest; Lower middle; Middle; Upper middle; Highest	Any period of lowest or lower middle; Consistently middle or higher
Current maternal education	Highest level of schooling obtained at the most recent interview	Less than secondary school; Secondary school graduation; Some post-secondary; College or University	Secondary school or less; Some post-secondary; College or University
Maternal age (at birth of child)	Mother's date of birth – child's date of birth	Continuous (number)	<20 years; ≥20 years
Maternal health	Health in general	Poor; Fair; Good; Very good; Excellent	Any period of poor or fair; Consistently good or better

Variable	Description	Scale of measurement	
		Original	Analysis
Maternal mental health	Based on Centre for Epidemiologic Studies-Depression Scale (35) (12 items)	Continuous (score of 0-36; high score = depressive symptoms)	Depressed (>90th %ile of standardized average across cycles); Not depressed
Social context: other			
Family functioning	Based on Chedoke-McMaster scale (36, 37) (12 items)	Continuous (score of 0-36; high score = family dysfunction)	Dysfunctional (>90th %ile of standardized average across cycles); Not dysfunctional
Proximal social processes			
Parenting interactions	Based on Parenting Practices Scale (38) (5 items – items vary depending on age of child)	Continuous (score of 0-20; low score = negative interactions)	Negative (<10th %ile of standardized average across cycles); Positive
Parenting effectiveness	Based on Parenting Practices Scale (38) (7 items – items vary depending on age of child)	Continuous (score of 0-28; high score = ineffective interactions)	Ineffective (>90th %ile of standardized average across cycles); Effective
Parenting consistency	Based on Parenting Practices Scale (38) (5 items – items vary depending on age of child)	Continuous (score of 0-20; low score = inconsistent interactions)	Inconsistent (<10th %ile of standardized average across cycles); Consistent
Other covariates			
Sex	Child sex	Male; Female	Male; Female

Variable	Description	Scale of measurement	
		Original	Analysis
Developmental outcomes			
Developmental delay at 2-3 years	Motor and Social Development Scale (39) (15 items – items vary depending on age of child)	Continuous (age-standardized with mean of 100, SD of 15)	Delayed (>1 SD below age-standardized mean); not delayed
Receptive vocabulary delay at 4-5 years	Peabody Picture Vocabulary Test (40) (in-person interview)	Continuous (age-standardized with mean of 100, SD of 15)	Delayed (>1 SD below age-standardized mean); not delayed
Design variables			
Cycle of entry into the NLSCY	0-1 years at Cycle 2, Cycle 3, Cycle 4, Cycle 5, or Cycle 6	Cycle 2; Cycle 3; Cycle 4; Cycle 5; Cycle 6	Cycle 2; Cycle 3; Cycle 4; Cycle 5; Cycle 6
Province of residence	Province of residence at time of most recent interview	NL, PEI, NS, NB, QC, ON, MB, SK, AB, BC	NL, PEI, NS, NB, QC, ON, MB, SK, AB, BC
Urban/rural status	Size of area of child's residence according to 2006 Canadian Census	Rural area; Urban <30,000; Urban 30,000-99,999; Urban 100,000-499,999; Urban 500,000/>	Rural area; Urban <30,000; Urban 30,000 or greater

Table B.7. NLSCY Questionnaire Items (1).

Construct	Responses	Items
Maternal mental health	Rarely or none of the time; Some or a little of the time; Occasionally or a moderate amount of the time; Most of the time	1. I did not feel like eating; my appetite was poor. 2. I felt that I could not shake off the blues even with help from family or friends. 3. I had trouble keeping my mind on what I was doing. 4. I felt depressed. 5. I felt that everything I did was an effort. 6. I felt hopeful about the future. 7. My sleep was restless. 8. I was happy. 9. I felt lonely. 10. I enjoyed life. 11. I had crying spells. 12. I felt that people disliked me.
Family functioning	Strong agree; Agree; Disagree; Strongly disagree	1. Planning family activities is difficult because we misunderstand each other. 2. In times of crisis, we turn to each other for support. 3. We cannot talk to each other about sadness we feel. 4. Individuals in the family are accepted for what they are. 5. We avoid discussions about our fears or concerns. 6. We express feelings to each other. 7. There are lots of bad feelings in our family. 8. In our family, we feel accepted for what we are. 9. Making decisions is a problem for our family. 10. We are able to make decisions about how to solve problems. 11. We don't get along well together. 12. We confide in each other.
Parenting interactions (0-5 years)	Never; About once a week or less; A few times a week; 1/> times a day; Many times each day	1. How often do you praise this child, by saying something like "Good for you!" or "What a nice thing you did!" or "That's good going!"? 2. How often do you and this child talk or play with each other, focusing attention on each other for five minutes or more, just for fun? 3. How often do you and this child laugh together? 4. How often do you do something special with this child that he/she enjoys? 5. How often do you play sports, hobbies, or games with this child?

Construct	Responses	Items
Parenting effectiveness (0-1 years)	Never; About once a week or less; A few times a week; 1/> times a day; Many times each day	1. How often do you get annoyed with this child for saying or doing something he/she is not supposed to? 2. How often do you tell this child that he/she is bad or not as good as others?
Parenting effectiveness (2-5 years)	Never; Less than half the time; About half the time; More than half the time; All the time	1. How often do you get annoyed with this child for saying or doing something he/she is not supposed to? 2. Of all the time that you talk to this child about his/her behaviour, what proportion is praise? 3. Of all the time that you talk to this child about his/her behaviour, what proportion is disapproval? 4. How often do you get angry when you punish this child? 5. How often do you think that the kind of punishment you give this child depends on your mood? 6. How often do you feel you are having problems managing this child in general? 7. How often do you have to discipline this child repeatedly for the same thing?
Parenting consistency (0-5 years)	Never; Less than half the time; About half the time; More than half the time; All the time	1. When you give this child a command or order to do something, what proportion of the time do you make sure he/she has done it? 2. If you tell this child he/she will get punished if he/she doesn't stop doing something, and he/she keeps doing it, how often will you punish him/her? 3. How often does this child get away with things for which you feel he/she should have been punished? 4. How often is this child able to get out of a punishment when he/she really sets his/her mind to it? 5. How often when you discipline this child, does he/she ignore the punishment?
Motor and social development (2-3 years)	Yes; No	1. Has this child ever let someone know, without crying, that wearing wet (soiled) pants or diapers bothered him/her? 2. Has he/she ever spoken a partial sentence of 3 words or more? 3. Has he/she ever walked up stairs by himself/herself without holding on to a rail

Construct	Responses	Items
(continued)		4. Has he/she ever washed and dried his/her hands without any help except for turning the water on and off? 5. Has he/she ever counted 3 objects correctly? 6. Has he/she ever gone to the toilet alone? 7. Has he/she ever walked up stairs by himself/herself with no help, stepping on each step with only one foot? 8. Does he/she know his/her own age and sex? 9. Has this child ever said the names of at least 4 colours? 10. Has this child ever pedalled a tricycle at least 10 feet? 11. Has this child ever done a somersault without help from anybody? 12. Has this child ever dressed himself/herself without any help except for tying shoes (and buttoning the backs of outfits)? 13. Has this child ever said his/her first name and last name together without someone's help? (Nickname may be used for first name.) 14. Has this child ever counted out loud up to 10? 15. Has this child ever drawn a picture of a man or woman with at least 2 parts of the body other than a head?

B.3 Data Management and Cleaning

B.3.1 Data Cleaning

Because coding quality in NLSCY data files is checked prior to the files' release, there are rarely problems with inappropriate characters or out-of-range values in the available files. Methods used by Statistics Canada to ensure accuracy of data included edits and flags built into the CATI and CAPI systems (e.g., review screens, range edits for numeric values, flow pattern and consistency edits); deletion of duplicate files and files with a high percentage of missing data; verification of age and gender; and consistency edits of final data using LogiPlus software (1).

Data were imported into SAS 9.3 (41) for data cleaning and analysis. Consistency of age and sex across cycles was verified. There were no inconsistencies in sex; a handful of inconsistencies in age could be explained by flipping of birth month and day across cycles. Consistency of responses across questions which were logically linked (e.g., yes/no questions and follow-up questions) was also verified.

B.3.2 Missing Data

Data in the NLSCY may be missing if (a) the respondent refuses to answer a question or (b) the respondent drops out of the sample before the end of the survey. Table B.8 shows the percentage of missing data for each variable across ages of data collection.

Table B.8. Missing Values for Variables Included in Chapter 4.

	0-1 years N (%)	2-3 years N (%)	4-5 years N (%)
Perinatal variables			
Smoking during pregnancy	292.5 (1.6)	---	---
Alcohol during pregnancy	295.3 (1.6)	---	---
Placental ischemia and other hypoxia	293.6 (1.6)	---	---
Other biological determinants	295.1 (1.6)	---	---
Delivery mode	<5.0 (---)	---	---
Gestational age			
Gestational age	0.0 (0.0)	---	---
Neonatal and infant variables			
Neonatal special care	7.6 (0.0)	---	---
Breastfeeding	---	580.1 (3.8)	---
Social context: family structure			
Maternal partnership status	41.3 (0.2)	0.0 (0.0)	0.0 (0.0)
Number of siblings	---	0.0 (0.0)	0.0 (0.0)
Social context: family resources			
Family income adequacy	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)
Current maternal education	---	462.5 (3.1)	609.5 (5.0)
Maternal age (at birth of child)	---	0.0 (0.0)	0.0 (0.0)
Maternal health	550.6 (3.0)	685.7 (4.5)	678.5 (5.5)
Maternal mental health	1,090.9 (5.9)	1,411.4 (9.4)	1,393.6 (11.3)
Social context: other			
Family functioning	1,000.3 (5.4)	1,270.6 (8.4)	1,326.6 (10.8)
Proximal social processes			
Parenting interactions	262.5 (1.4)	392.9 (2.6)	437.7 (3.6)
Parenting effectiveness	178.2 (1.0)	608.3 (4.0)	768.6 (6.3)
Parenting consistency	---	819.5 (5.4)	1,031.8 (8.4)
Other covariates			
Child sex	---	0.0 (0.0)	0.0 (0.0)

--- : Not included in analysis.

B.4 Statistical Analyses

Please refer to Appendix A.4.1 for a description of modified Poisson regression, Appendix A.4.2 for a description of blockwise model building, and Appendix A.4.5 for a description of additive interaction. All descriptions apply to Chapter 4 with some nuances, described below.

B.4.1 Weights

The stratification and clustering of the NLSCY survey design results in unequal probabilities of selection for survey participants. Because of this complex sampling design as well as unequal probabilities of non-response, the distribution of characteristics in the sample may differ from their distributions in the population. These population distributions are maintained by applying survey weights, which account for the sampling design and non-response (42).

Children are initially assigned cross-sectional weights. Children who are involved in longitudinal follow-up are also assigned longitudinal weights when they respond at each subsequent cycle. Both types of weights take into account the child's design weight (i.e., the inverse probability of selection into the NLSCY) and are adjusted for non-response and post-stratification. The non-response adjustment ensures that the design weight is inflated so that the weights for respondents add up to the sum of the original design weights for the whole sample (respondents and non-respondents). The size of this adjustment is determined by calculating a unique inflation factor for groups of individuals with similar likelihoods of responding (i.e., response homogeneous groups). The post-stratification adjustment ensures that the sum of weights matches population totals by age, sex, and province (1).

For the current study, longitudinal weights (Cycles 2 through 6) or longitudinal funnel weights (Cycles 7 and 8) were used for all estimates (i.e., descriptive, univariable, and multivariable). (Funnel weights were assigned to children studied longitudinally who responded at each cycle. Prior to Cycle 7, only ECD children who replied to the previous cycle were eligible to be surveyed. Therefore, the longitudinal funnel weights for Cycles

7 and 8 correspond to the longitudinal weights used previously.) These weights were normalized to maintain the original sample size of each cycle by dividing the survey weight for each child by the mean of the survey weight for all analyzed children in that cycle (1). (This was done to avoid over-estimation of statistical significance.)

B.4.2 Bootstrapping

Although weights take into account some aspects of the survey design, weighted analyses are considered to be an "incomplete implementation of the design-based approach" because weights do not account for the non-independence of sampled units (43). Because of the clustered nature of sampling, the "effective number" of units in the sample is smaller than the actual number of units due to the correlations among sampled units. These correlations affect the estimation of sampling error, and, thus, the variance of estimates (1).

Bootstrapping is a replication method which consists of estimating the variance of a population parameter by re-sampling, with replacement, from the study sample. The variability among the estimates that are calculated from this process are used to estimate the true sampling error of the full-sample estimate (44). For the NLSCY and other population-based surveys with complex sampling designs, this re-sampling is accomplished with bootstrap weights. The NLSCY has a set of 1,000 bootstrap weights from which 1,000 estimates can be used to compute the variance for an estimator. There are several options for performing this, including a SAS macro (BOOTVAR) (45), which can only be used for linear regression and logistic regression. Other options include using SUDAAN (for linear, logistic, generalized logit, proportional odds, Poisson, and log-linear regression) and Stata (for linear, interval, logistic, probit, generalized logit, proportional odds, ordered probit, Poisson, and log-linear regression) (46).

Because statistical packages with bootstrapping capabilities have not yet been developed for modified Poisson regression, the sampling design was taken into account in the current multivariable analyses by controlling for province and urban/rural status, two variables used in the NLSCY sampling design. Furthermore, since the dataset includes five pooled cycles for any given age group, a "year" variable was entered into the models

to control for the cycle of entry into the NLSCY. These variables were included in the analyses at all stages of model building. Although this approach, called a "quasi model-based approach" to variance estimation, does not completely account for non-independence among units, this was a compromise which allowed us to (a) use a regression model that directly produces unbiased relative risks and that could be used to assess additive interaction and (b) acknowledge the complex sampling design of the NLSCY.

B.4.3 Population Attributable Fractions

The population attributable fraction (**PAF**) is defined as the proportion of the incidence in the outcome that is expected to be reduced (in the whole population) if the exposure is eliminated (47). The traditional formula, which is based on the proportion exposed in the whole population and the relative risk for the association between the exposure and the outcome, is biased if the relative risk is adjusted for confounders (47). A more suitable equation, proposed by Kleinbaum et al. (48) and described by Rockhill et al. (47), instead uses the proportion exposed among those with the outcome and the adjusted relative risk:

$$PAF = \frac{P_c\,(aRR - 1)}{aRR}$$

(Equation B1)

where:

P_c Is the exposure prevalence among cases.

aRR Is the adjusted relative risk.

This formula was used to calculate the population attributable fractions in Chapter 4, thus enabling the use of adjusted relative risks for unbiased estimates.

B.5 Frequencies of Components of Derived Variables

Several variables in the analyses for Chapter 4 were composites of variables thought to reflect the same underlying concept. The following tables show the frequencies of the components of each of the derived variables. These tables contain information on the biological determinants of preterm birth (Table B.9) and neonatal morbidity (Table B.10), Table B.11 shows patterns in transitions in variables measured longitudinally where transitions into or out of risk across time were aggregated into “any transition” or into “any period of risk.”

Table B.9. Prevalence of Conditions Included in the Biological Determinants of Preterm Birth in the Chapter 4 Sample (N=15,099 at 2-3 Years of Age; N=12,203 at 4-5 Years of Age).

	Weighted at 2-3 years		Weighted at 4-5 years	
	N	%	N	%
Placental ischemia and other hypoxia				
Small for gestational age				
Yes	468.3/14,883.8	3.1	369.2/12,152.0	3.0
No	14,415.5/14,883.8	96.9	11,782.9/12,152.0	97.0
Pregnancy hypertension				
Yes	1,466.7/14,883.8	9.9	1,216.1/12,152.0	10.0
No	13,417.1/14,883.8	90.1	10,935.9/12,152.0	90.0

Table B.10. Prevalence of Conditions Included in Neonatal Special Care in the Chapter 4 Sample (N=15,099 at 2-3 Years of Age; N=12,203 at 4-5 Years of Age).

	Weighted at 2-3 years		Weighted at 4-5 years	
	N	%	N	%
Neonatal special care				
NICU admission				
Yes	735.0/15,092.1	4.9	575.5/12,298.3	4.7
No	14,357.1/15,092.1	95.1	11,723.2/12,298.3	95.3
Transfer to specialized hospital				
Yes	111.7/15,092.1	0.7	89.2/12,298.3	0.7
No	14,980.4/15,092.1	99.3	12,209.2/12,298.3	99.3
Ventilation				
Yes	630.3/15,092.1	4.2	502.8/12,298.3	4.1
No	14,461.8/15,092.1	94.8	11,795.5/12,298.3	95.9

Table B.11. Patterns of Transitions in Variables Measured Longitudinally in the Chapter 4 Sample (N=15,099 at 2-3 Years of Age; N=12,203 at 4-5 Years of Age).

	Weighted at 2-3 years		Weighted at 4-5 years	
	N	%	N	%
Maternal partnership status				
Consistently one parent	1,340.8/15,099.0	8.9	873.9/12,302.0	7.1
One to two parent	283.3/15,099.0	1.9		
One to one to two parent			235.2/12,302.0	1.9
One to two to two parent			169.3/12,302.0	1.4
One to two to one parent			64.9/12,302.0	0.5
Two to one parent	619.4/15,099.0	4.1		
Two to two to one parent			470.6/12,302.0	3.8
Two to one to one parent			411.7/12,302.0	3.4
Two to one to two parent			109.0/12,302.0	0.9
Consistently two parent	12,855.5/15,099.0	85.1	9,967.5/12,302.0	81.0
Income adequacy				
Consistently inadequate	999.8/15,099.0	6.6	422.2/12,302.0	3.4
Inadequate to adequate	1,185.0/15,099.0	7.9		
Inadequate to inadequate to adequate			397.3/12,302.0	3.2
Inadequate to adequate to adequate			718.6/12,302.0	5.8
Inadequate to adequate to inadequate			191.1/12,302.0	1.6
Adequate to inadequate	583.4/15,099.0	3.9		
Adequate to adequate to inadequate			271.8/12,302.0	2.2
Adequate to inadequate to inadequate			127.3/12,302.0	1.1
Adequate to inadequate to adequate			337.5/12,302.0	2.7
Consistently adequate	12,330.8/15,099.0	81.6	9,835.7/12,302.0	80.0
Maternal health				
Consistently poor	222.2/14,413.3	1.5	46.3/11,623.5	0.4
Poor to good	333.4/14,413.3	2.3		
Poor to poor to good			97.3/11,623.5	0.8
Poor to good to good			231.7/11,623.5	2.0
Poor to good to poor			307.5/11,623.5	2.7
Good to poor	501.9/14,413.3	3.5		
Good to good to poor			332.6/11,623.5	2.9
Good to poor to poor			106.2/11,623.5	0.9
Good to poor good			84.5/11,623.5	0.7
Consistently good	13,355.9/14,413.3	92.7	10,417.4/11,623.5	89.6

B.6 Multicollinearity Analyses for Chapter 4

Similar to Chapter 3 and Chapter 5, multicollinearity was assessed prior to multivariable analyses using polychoric correlations (Table B.12) and linear regression methods (PROC REG VIF and TOL) (Table B.13). Refer to Appendix A.6 for a full description of these approaches. As can be seen in Table B.13, none of the values in the current study exceeded the allowable thresholds. Note that because the covariates included in the developmental delay analysis and the receptive vocabulary delay analysis were the same and because tests of multicollinearity focus on the relationships among covariates (not with the outcome), we did not repeat multicollinearity tests for both analyses.

Table B.12. Polychoric Correlations among Covariates for Chapter 4 Analyses.

	1	2	3	4	5	6	7	8	9	10	11
1		0.07	0.11	0.04	-0.04	0.07	**0.41**	-0.05	0.38	0.42	0.32
2			-0.04	-0.08	-0.04	-0.05	0.00	0.01	-0.09	-0.14	-0.10
3				0.13	0.10	0.11	0.09	-0.19	0.06	0.08	0.14
4					0.16	0.17	0.01	0.01	0.06	0.07	-0.16
5						0.18	-0.05	-0.11	-0.03	-0.02	-0.08
6							-0.01	0.00	0.00	0.00	-0.05
7								-0.26	**0.78**	0.33	**0.53**
8									-0.02	0.04	-0.36
9										**0.42**	**0.57**
10											**0.54**

	12	13	14	15	16	17	18	19	20	21
1	0.27	0.28	0.17	-0.04	0.01	0.20	0.01	-0.12	-0.09	-0.08
2	-0.02	0.04	-0.04	0.10	0.04	-0.04	0.01	0.06	-0.11	0.00
3	0.17	0.07	0.07	-0.03	-0.02	0.05	0.01	-0.04	0.00	-0.01
4	0.16	0.11	0.07	0.03	0.00	-0.01	0.04	0.04	-0.02	-0.01
5	0.04	0.03	0.06	-0.01	0.02	0.00	0.03	0.00	0.00	0.09
6	0.05	0.02	0.03	0.00	-0.04	0.01	0.03	-0.01	-0.01	0.03
7	0.32	**0.40**	0.33	0.06	0.09	0.15	-0.02	0.05	-0.01	0.01
8	-0.02	0.01	-0.07	0.19	0.04	0.03	-0.01	-0.12	0.03	-0.06
9	0.34	0.39	0.30	0.13	0.05	0.25	-0.02	-0.04	-0.04	-0.11
10	0.25	0.24	0.20	0.09	0.07	0.20	0.00	-0.16	0.03	-0.05
11	0.13	0.17	0.25	-0.01	0.06	0.14	0.02	-0.08	-0.02	-0.04
12		**0.53**	0.29	0.05	0.10	0.04	-0.04	-0.03	0.00	0.03
13			**0.55**	0.16	0.23	0.24	-0.02	-0.03	-0.03	0.17
14				0.20	0.24	0.21	0.01	0.01	0.04	-0.02
15					0.14	0.21	-0.01	0.01	-0.06	-0.12
16						0.20	0.12	0.02	0.07	0.07

	12	13	14	15	16	17	18	19	20	21
17							-0.02	-0.01	-0.11	-0.11
18								-0.01	-0.01	-0.01
19									0.13	-0.02
20										-0.01
21										

* These analyses were conducted using the 2-3 year old sample. They were also conducted in the 4-5 year old sample, and similar results were found. Since the focus is on the relationships among the predictor variables, and the 4-5 year old sample is a subset of the 2-3 year old sample, the results for 4-5 year olds are not presented.

1 = smoking during pregnancy, 2 = alcohol use during pregnancy, 3 = placental ischemia and other hypoxia, 4 = other biological determinants of preterm birth, 5 = delivery mode, 6 = gestational age, 7 = maternal partnership status, 8 = number of siblings, 9 = family income adequacy, 10 = current maternal education, 11 = maternal age, 12 = maternal health, 13 = maternal mental health, 14 = family functioning, 15 = parenting interactions, 16 = parenting effectiveness, 17= parenting consistency, 18 = infant sex, 19 = urbanicity, 20 = province, 21 = cycle.

Table B.13. Tolerance, Variance Inflation Factor, Eigenvalue, and Condition Index for Covariates for Chapter 4 Analyses.

Variable[1]	Variance Inflation Factor [2]	Tolerance[3]	Eigenvalue[4]	Condition index[5]
Intercept	.	0	.	.
Smoking during pregnancy	0.88	1.14	2.45	1.00
Alcohol use during pregnancy	0.95	1.05	1.86	1.15
Placental ischemia and other hypoxia	0.97	1.03	1.53	1.26
Other biological determinants of preterm birth	0.97	1.03	1.44	1.30
Caesarean delivery	0.96	1.04	1.39	1.33
Late preterm gestational age	0.95	1.05	1.33	1.35
Early term gestational age	0.95	1.06	1.28	1.38
Consistent single partnership status	0.70	1.42	1.23	1.41
Any transition in partnership status	0.84	1.19	1.21	1.42
3 or more siblings	0.79	1.27	1.16	1.45
1-2 siblings	0.78	1.28	1.13	1.47
Any period of inadequate family income	0.63	1.58	1.12	1.48
Maternal education secondary school or less	0.75	1.33	1.11	1.48
Maternal education some post-secondary	0.86	1.17	1.05	1.53
Maternal age <20 years	0.89	1.13	1.04	1.53
Poor maternal health	0.91	1.10	1.04	1.53
Poor maternal mental health	0.83	1.20	1.02	1.55
Poor family functioning	0.88	1.13	1.02	1.55
Negative parenting interactions	0.96	1.04	1.01	1.56
Ineffective parenting	0.96	1.04	1.00	1.57
Inconsistent parenting	0.95	1.05	0.97	1.59
Male sex	0.99	1.01	0.96	1.60
Urban up to 30,000	0.52	1.94	0.92	1.63
Urban 30,000 or more	0.50	2.01	0.90	1.65
NL	0.87	1.15	0.89	1.66
PEI	0.96	1.04	0.85	1.69
NS	0.81	1.24	0.84	1.70
NB	0.84	1.19	0.82	1.72
QC	0.43	2.32	0.77	1.79
MB	0.77	1.29	0.66	1.93

Variable[1]	Tolerance[2]	Variance Inflation Factor[3]	Eigenvalue[4]	Condition index[5]
SK	0.79	1.26	0.60	2.02
BC	0.56	1.79	0.52	2.17
Cycle 3	0.59	1.70	0.39	2.49
Cycle 4	0.72	1.38	0.30	2.87
Cycle 5	0.69	1.45	0.28	2.95
Cycle 6	0.68	1.47	0.16	3.97

* These analyses were conducted using the 2 to 3 year old sample. They were also conducted in the 4 to 5 year old sample, and similar results were found. Since the focus is on the relationships among the predictor variables, and the 4 to 5 year old sample is a subset of the 2 to 3 year old sample, the results for 4 to 5 year olds are not presented.

[1] Only the level of the dummy variable under analysis is shown (e.g., "full term gestational age" not shown).

[2] Measures the inflation in the variances of the parameter estimates due to collinearities among predictors; >10 = problematic.

[3] = 1 / VIF; measures the tolerance values for parameter estimates and reflects the degree of multicollinearity; <0.10 = problematic.

[4] The variance of the covariates; Near 0 = problematic.

[5] The square root of ratio of the largest eigenvalue to each individual eigenvalue; reflects the instability in the model; >10 = problematic.

B.7 Additional Analyses for Chapter 4

B.7.1 Regression Diagnostics

Regression diagnostics were performed to test for outliers and influential observations in the final multivariable models. Because regression diagnostic procedures have not been developed for modified Poisson regression, these were performed using logistic regression using the methods described in Appendix A.7.1. There were several influential observations in the receptive vocabulary delay analysis. Because the number was less than 5, the specifics cannot be released by Statistics Canada. These observations were removed, and the results for the regression diagnostics after removal of the influential observations are in Table B.14. For developmental delay, C statistic values ranged from <0.01 to 0.96. For receptive vocabulary delay, C statistic values ranged from <0.01 to 0.98.

B.7.2 Model Building Steps

The steps used to perform blockwise model building are shown in Table B.15 (developmental delay) and Table B.16 (receptive vocabulary delay).

B.7.3 Addition of Neonatal and Infant Variables to Multivariable Models

Neonatal special care and breastfeeding were considered to be pathway variables and were therefore not included in the multivariable models for Chapter 4. However, because it may be important to estimate the effects of gestational age above and beyond the intermediary effects of these variables, we conducted a sensitivity analysis in which we controlled for neonatal special care and breastfeeding in the multivariable analyses of developmental delay (Table B.17) and receptive vocabulary delay (Table B.18). The adjusted relative risks for gestational age remained essentially unchanged.

B.7.4 Loss to Follow-Up

As described in Chapter 4, by 2 to 3 years, 18.5% of the original sample had been lost to follow-up or excluded. By 4 to 5 years, 33.6% of the original sample had been lost to follow-up or excluded. Children not measured at 2 to 3 years of age or 4 to 5 years of age

were more likely to have social risk factors, including single parent families, income inadequacy, low maternal education, poor maternal mental health, and poor family functioning. Refer to Table B.19 for a summary of differences between respondents and non-respondents at 2 to 3 years of age and Table B.20 for a summary of differences between respondents and non-respondents at 4 to 5 years of age.

Table B.14. DFbetas for Final Multivariable Models (Chapter 4).

	Range	No. >2
Developmental delay		
Caesarean section	-0.14, 0.45	0
Late preterm gestational age	-0.16, 0.35	0
Early term gestational age	-0.25, 0.46	0
3 or more siblings	-0.16, 0.29	0
1-2 siblings	-0.03, 0.31	0
Any period of inadequate family income	-0.29, 0.14	0
Secondary education or less	-0.20, 0.29	0
Some post-secondary education	-0.24, 0.30	0
Any period of maternal depression	-0.15, 0.41	0
Negative parenting interactions	-0.22, 0.45	0
Ineffective parenting	-0.23, 0.30	0
Inconsistent parenting	-0.16, 0.43	0
Male sex	-0.17, 0.58	0
Receptive vocabulary delay[1]		
Alcohol during pregnancy	-0.14, 0.44	0
Placental ischemia and other hypoxia	-0.21, 0.47	0
Other biological determinants	-0.18, 0.30	0
Late preterm gestational age	-0.24, 0.53	0
Early term gestational age	-0.24, 0.35	0
3 or more siblings	-0.15, 0.29	0
1-2 siblings	-0.32, 0.44	0
Any period of inadequate family income	-0.42, 0.16	0
Secondary education or less	-0.22, 0.41	0
Some post-secondary education	-0.24, 0.32	0
Any period of poor maternal health	-0.15, 0.41	0
Any period of maternal depression	-0.19, 0.45	0
Poor family functioning	-0.26, 0.41	0
Negative parenting interactions	-0.17, 0.55	0
Ineffective parenting	-0.22, 0.45	0
Inconsistent parenting	-0.19, 0.48	0
Male sex	-0.19, 0.35	0

* Only the level of the dummy variable under analysis is shown (e.g., "full term gestational age" not shown).

[1] The values for the receptive vocabulary analysis include DFbetas after removal of the <5 influential observations. There were no influential observations for the developmental delay analysis.

Table B.15. Model Building Steps for Developmental Delay Multivariable Model (Chapter 4).

	Univar. RR (p)	Block 1 RR (p)	Block 2 RR (p)	Block 3 RR (p)	Block 4 RR (p)	Block 5 RR (p)	Block 6 RR (p)	Block 7 RR (p)
Perinatal variables								
Smoking during pregnancy								
Yes	1.10 (.21)	1.12 (.14)	1.11 (.15)	1.12 (.14)	1.03 (.76)			
No								
Alcohol during pregnancy								
Yes	0.99 (.88)	0.93 (.39)						
No								
Placental ischemia and other hypoxia								
Yes	1.08 (.49)	1.06 (.48)						
No								
Other biological determinants								
Yes	1.15 (.29)	1.08 (.53)						
No								
Delivery mode								
Caesarean	1.24 (<.01)	1.22 (<.01)	1.22 (<.01)	1.24(<.01)	1.24 (<.01)	1.21 (.01)	1.21 (.01)	1.19 (.02)
Vaginal								
Gestational age								
Gestational age								
Late preterm	1.26 (.04)		1.19 (.13)	1.20 (.11)	1.13 (.29)	1.18 (.15)	1.18 (.17)	1.13 (.29)
Early term	1.07 (.32)		1.05 (.47)	1.04 (.53)	1.14 (.07)	1.13 (.09)	1.13 (.11)	1.11 (.15)
Full term								

	Univar. RR (p)	Block 1 RR (p)	Block 2 RR (p)	Block 3 RR (p)	Block 4 RR (p)	Block 5 RR (p)	Block 6 RR (p)	Block 7 RR (p)
Social context variables: family structure								
Maternal partnership status								
Single parent	1.04 (.78)			1.09 (.45)				
Any transition	0.91 (.46)			0.92 (.55)				
Two parent								
No. of siblings								
3 or more	1.48 (<.01)			1.51 (<.01)	1.46 (<.01)	1.48 (<.01)	1.36 (.01)	1.36 (.01)
1-2	1.24 (<.01)			1.25 (<.01)	1.25 (<.01)	1.25 (<.01)	1.19 (.03)	1.18 (.05)
None								
Social context variables: family resources								
Family income adequacy								
Inadequate	1.22 (<.01)				1.19 (.06)	1.17 (.08)	1.13 (.15)	1.15 (.10)
Adequate								
Current maternal education								
Secondary /<	1.35 (<.01)				1.34 (<.01)	1.32 (<.01)	1.29 (<.01)	1.27 (<.01)
Some post-secondary	0.97 (.71)				0.96 (.64)	0.96 (.65)	0.94 (.53)	0.96 (.66)
College or university								
Maternal age								
<20 years	0.94 (.70)				0.89 (.54)			
≥20 years								
Maternal health								
Poor	1.04 (.66)				0.91 (.40)			
Good								

	Univar. RR (p)	Block 1 RR (p)	Block 2 RR (p)	Block 3 RR (p)	Block 4 RR (p)	Block 5 RR (p)	Block 6 RR (p)	Block 7 RR (p)
Maternal mental health								
Depressed	1.34 (<.01)				1.22 (.05)	1.15 (.20)	1.15 (.17)	1.17 (.13)
Not depressed								
Social context variables: other								
Family functioning								
Poor functioning	1.21 (.03)					1.10 (.35)		
Not poor								
Proximal social processes								
Parenting interactions								
Negative	1.63 (<.01)						1.40 (<.01)	1.40 (<.01)
Positive								
Parenting effectiveness								
Ineffective	1.22 (.03)						1.24 (.02)	1.14 (.16)
Effective								
Parenting consistency								
Inconsistent	1.55 (<.01)						1.28 (.02)	1.32 (<.01)
Consistent								
Other covariates								
Child sex								
Male	2.25(<.01)							2.36 (<.01)
Female								

*Block 7 is also the final model.

Table B.16. Model Building Steps for Receptive Vocabulary Delay Multivariable Model (Chapter 4).

	Univar. RR (p)	Block 1 RR (p)	Block 2 RR (p)	Block 3 RR (p)	Block 4 RR (p)	Block 5 RR (p)	Block 6 RR (p)	Block 7 RR (p)
Perinatal variables								
Smoking during pregnancy								
Yes	1.13 (.21)	1.06 (.53)						
No								
Alcohol during pregnancy								
Yes	0.60 (<.01)	0.56 (<.01)	0.56 (<.01)	0.57 (<.01)	0.63 (<.01)	0.64 (<.01)	0.59 (<.01)	0.60 (<.01)
No								
Placental ischemia and other hypoxia								
Yes	1.37 (<.01)	1.31 (<.01)	1.32 (<.01)	1.34 (<.01)	1.23 (.05)	1.22 (.06)	1.23 (.07)	1.24 (.06)
No								
Other biological determinants								
Yes	1.67 (<.01)	1.59 (<.01)	1.59 (<.01)	1.59 (<.01)	1.46 (<.01)	1.37 (.03)	1.40 (.02)	1.42 (.02)
No								
Delivery mode								
Caesarean	1.01 (.90)	1.01 (.94)						
Vaginal								
Gestational age								
Gestational age								
Late preterm	1.03 (.83)		0.97 (.80)	0.98 (.88)	1.02 (.87)	1.06 (.66)	1.09 (.56)	1.06 (.68)
Early term	1.09 (.33)		1.05 (.56)	1.06 (.50)	1.09 (.33)	1.09 (.38)	1.05 (.61)	1.03 (.76)
Full term								

	Univar. RR (p)	Block 1 RR (p)	Block 2 RR (p)	Block 3 RR (p)	Block 4 RR (p)	Block 5 RR (p)	Block 6 RR (p)	Block 7 RR (p)
Social context variables: family structure								
Maternal partnership status								
Single parent	1.01 (.94)			1.03 (.84)				
Any transition	1.18 (.39)			1.23 (.28)				
Two parent								
No. of siblings								
3 or more	1.62 (<.01)			1.88 (<.01)	1.86 (<.01)	1.90 (<.01)	1.80 (<.01)	1.81 (<.01)
1-2	0.99 (.94)			1.07 (.54)	1.13 (.28)	1.12 (.34)	1.06 (.61)	1.05 (.67)
None								
Social context variables: family resources								
Family income adequacy								
Inadequate	2.36 (<.01)				1.79 (<.01)	1.80 (<.01)	1.59 (<.01)	1.60 (<.01)
Adequate								
Current maternal education								
Secondary /<	2.11 (<.01)				1.43 (<.01)	1.46 (<.01)	1.48 (<.01)	1.47 (<.01)
Some post-secondary	1.34 (.02)				1.15 (.25)	1.17 (1.9)	1.18 (.19)	1.18 (.18)
College or university								
Maternal age								
<20 years	1.51 (<.01)				0.98 (.88)			
≥20 years								
Maternal health								
Poor	1.93 (<.01)				1.30 (.03)	1.29 (.04)	1.34 (.02)	1.36 (.01)
Good								

	Univar. RR (p)	Block 1 RR (p)	Block 2 RR (p)	Block 3 RR (p)	Block 4 RR (p)	Block 5 RR (p)	Block 6 RR (p)	Block 7 RR (p)
Maternal mental health								
Depressed	1.98 (<.01)				1.42(<.01)	1.42 (.01)	1.28 (.06)	1.26 (.08)
Not depressed								
Social context variables: other								
Family functioning								
Poor functioning	1.71 (<.01)					1.26 (.06)	1.34 (.02)	1.32 (.03)
Not poor								
Proximal social processes								
Parenting interactions								
Negative	1.72 (<.01)						1.30 (.03)	1.30 (.03)
Positive								
Parenting effectiveness								
Ineffective	1.17 (.18)						1.14 (.31)	1.13 (.34)
Effective								
Parenting consistency								
Inconsistent	1.85 (<.01)						1.48 (<.01)	1.51 (<.01)
Consistent								
Other covariates								
Child sex								
Male	1.33 (<.01)							1.51 (<.01)
Female								

* Block 7 is also the final model.

Table B.17. Weighted Developmental Delay Multivariable Model with Neonatal and Infant Pathway Variables Added (Chapter 4).

	% with delay	Unadjusted RR (95% CI)	Adjusted RR (95% CI)
Perinatal variables			
Smoking during pregnancy			
Yes	14.9	1.10 (0.95, 1.26)	---
No	13.6	reference	
Alcohol during pregnancy			
Yes	13.7	0.99 (0.84, 1.16)	---
No	13.9	reference	
Placental ischemia and other hypoxia			
Yes	14.6	1.06 (0.89, 1.26)	---
No	13.8	reference	
Other biological determinants			
Yes	15.8	1.15 (0.89, 1.48)	---
No	13.7	reference	
Delivery type			
Caesarean	16.4	1.24 (1.08, 1.42)	1.16 (0.99, 1.34)
Vaginal	13.3	reference	reference
Gestational age			
Gestational age			
Late preterm	16.7	1.26 (1.01, 1.56)	1.11 (0.88, 1.41)
Early term	14.3	1.07 (0.94, 1.22)	1.10 (0.95, 1.27)
Full term	13.3	reference	reference
Neonatal and infant variables			
Neonatal morbidity			
Yes	17.6	1.30 (1.08, 1.57)	1.09 (0.89, 1.38)
No	13.5	reference	reference
Breastfeeding			
None	16.6	1.42 (1.21, 1.68)	1.27 (1.06, 1.55)
≤6 months	14.7	1.27 (1.10, 1.45)	1.14 (0.99, 1.34)
>6 months	11.6	reference	reference
Social context variables: family structure			
Maternal partnership status			
Single parent family	14.4	1.04 (0.83, 1.29)	---
Any transition in partnership status	12.6	0.91 (0.70, 1.18)	
Two parent family	13.9	reference	
Number of siblings			
3 or more	17.3	1.48 (1.20, 1.83)	1.45 (1.15, 1.89)
1 to 2	14.4	1.24 (1.07, 1.43)	1.17 (1.00, 1.38)
None	11.6	reference	reference

	% with delay	Unadjusted RR (95% CI)	Adjusted RR (95% CI)
Social context variables: family resources			
Family income adequacy			
Any period of inadequacy	16.2	1.22 (1.05, 1.41)	1.11 (0.94, 1.38)
Consistently adequate	13.3	reference	reference
Current maternal education			
Secondary or less	16.8	1.34 (1.18, 1.54)	1.23 (1.06, 1.43)
Some post-secondary	12.1	0.97 (0.82, 1.15)	0.93 (0.77, 1.12)
College or university degree	12.5	reference	reference
Maternal age (at birth of child)			
<20 years	13.0	0.94 (0.67, 1.30)	---
20 years or older	13.9	reference	
Maternal health			
Any period of poor health	14.5	1.04 (0.86, 1.27)	---
Consistently good	13.9	reference	
Maternal mental health			
Any period of depression	18.0	1.34 (1.12, 1.61)	1.18 (0.96, 1.45)
Consistently not depressed	13.4	reference	reference
Social context variables: other			
Family functioning			
Poor functioning	16.4	1.21 (1.02, 1.44)	---
Not poor	13.5	reference	
Proximal social processes			
Parenting interactions			
Negative	21.1	1.63 (1.39, 1.91)	1.40 (1.17, 1.67)
Positive	13.0	reference	reference
Parenting effectiveness			
Ineffective	16.4	1.22 (1.02, 1.46)	1.15 (0.94, 1.38)
Effective	13.4	reference	reference
Parenting consistency			
Inconsistent	20.2	1.55 (1.29, 1.87)	1.30 (1.05, 1.60)
Consistent	13.1	reference	reference
Other covariates			
Child sex			
Male	19.0	2.25 (1.98, 2.56)	2.37 (2.05, 2.74)
Female	8.4	reference	reference

--- : p>.20 in final model.

* Analyses also control for design variables (cycle of entry into NLSCY, province, and urban/rural status).

Table B.18. Weighted Receptive Vocabulary Delay Multivariable Model with Neonatal and Infant Pathway Variables Added (Chapter 4).

	% with delay	Unadjusted RR (95% CI)	Adjusted RR (95% CI)
Perinatal variables			
Smoking during pregnancy			
Yes	14.4	1.13 (0.93, 1.36)	---
No	12.8	reference	
Alcohol during pregnancy			
Yes	8.4	0.60 (0.46, 0.77)	0.58 (0.44, 0.76)
No	14.0	reference	reference
Placental ischemia and other hypoxia			
Yes	17.1	1.37 (1.12, 1.69)	1.22 (0.98, 1.52)
No	12.5	reference	reference
Other biological determinants			
Yes	20.9	1.67 (1.30, 2.15)	1.39 (1.03, 1.89)
No	12.5	reference	reference
Delivery type			
Caesarean	13.2	1.01 (0.84, 1.22)	---
Vaginal	13.0	reference	
Gestational age			
Gestational age			
Late preterm	13.1	1.03 (0.79, 1.35)	1.12 (0.82, 1.52)
Early term	13.9	1.09 (0.91, 1.31)	1.04 (0.86, 1.27)
Full term	12.7	reference	reference
Neonatal and infant variables			
Neonatal morbidity			
Yes	13.8	1.07 (0.80, 1.42)	0.93 (0.71, 1.20)
No	13.0	reference	reference
Breastfeeding			
None	21.1	1.73 (1.41, 2.12)	1.31 (1.00, 1.70)
≤6 months	16.2	1.39 (1.15, 1.69)	1.14 (0.91, 1.42)
>6 months	11.9	reference	reference
Social context variables: family structure			
Maternal partnership status			
Single parent family	21.1	1.01 (0.73, 1.41)	---
Any transition in partnership status	16.2	1.18 (0.80, 1.74)	
Two parent family	11.9	reference	
Number of siblings			
3 or more	20.2	1.62 (1.24, 2.10)	1.89 (1.34, 2.66)
1 to 2	12.4	0.99 (0.80, 1.22)	1.09 (0.85, 1.41)
None	12.5	reference	reference

	% with delay	Unadjusted RR (95% CI)	Adjusted RR (95% CI)
Social context variables: family resources			
Family income adequacy			
Any period of inadequacy	24.5	2.35 (2.01, 2.77)	1.59 (1.28, 1.97)
Consistently adequate	10.4	reference	reference
Current maternal education			
Secondary or less	19.4	2.11 (1.78, 2.50)	1.44 (1.16, 1.78)
Some post-secondary	12.4	1.34 (1.05, 1.71)	1.16 (0.89, 1.49)
College or university degree	9.2	reference	reference
Maternal age (at birth of child)			
<20 years	20.3	1.59 (1.20, 2.11)	---
20 years or older	12.8	reference	
Maternal health			
Any period of poor health	21.9	1.93 (1.56, 2.40)	1.32 (1.02, 1.71)
Consistently good	11.4	reference	reference
Maternal mental health			
Any period of depression	21.5	1.99 (1.61, 2.45)	1.25 (0.97, 1.64)
Consistently not depressed	10.8	reference	reference
Social context variables: other			
Family functioning			
Poor functioning	19.3	1.71 (1.38, 2.11)	1.31 (1.02, 1.69)
Not poor	11.3	reference	reference
Proximal social processes			
Parenting interactions			
Negative	20.3	1.72 (1.40, 2.13)	1.33 (1.05, 1.68)
Positive	11.8	reference	reference
Parenting effectiveness			
Ineffective	14.6	1.17 (0.93, 1.48)	1.17 (0.90, 1.50)
Effective	12.4	reference	reference
Parenting consistency			
Inconsistent	21.8	1.85 (1.53, 2.24)	1.48 (1.17, 1.86)
Consistent	11.8	reference	reference
Other covariates			
Child sex			
Male	14.9	1.33 (1.14, 1.56)	1.49 (1.24, 1.77)
Female	11.2	reference	reference

--- : p>.20 in final model.

* Analyses also control for design variables (cycle of entry into NLSCY, province, and urban/rural status).

Table B.19. Comparison of Respondents and Non-Respondents at 2-3 Years on Baseline Characteristics (Chapter 4).

	Respondents		Non-respondents		
	N	%	N	%	p-value
Perinatal variables					
Smoking during pregnancy					
Yes	2,568.4/14,569.1	17.6	738.1/3,669.3	20.1	<.001
No	12,000.7/14,569.1	82.4	2,931.2/3,669.3	79.9	
Alcohol during pregnancy					
Yes	2,302.8/14,566.4	15.8	513.7/3,669.3	14.0	.01
No	12,263.6/14,566.4	84.2	3,155.6/3,669.3	86.0	
Placental ischemia and other hypoxia					
Yes	1,824.4/14,569.3	12.5	461.7/3,688.0	12.6	.92
No	12,744.9/14,569.3	87.5	3,206.3/3,668.0	87.4	
Other biological determinants					
Yes	913.1/14,568.3	6.3	223.0/3,667.7	6.1	.68
No	13,655.2/14,568.3	93.7	3,444.7/3,667.7	93.9	
Delivery mode					
Caesarean	2,839.5/14,527.1	19.2	718.0/3,757.9	19.1	.87
Vaginal	11,687.6/14,527.1	80.8	3,039.9/3,757.9	80.9	
Gestational age					
Gestational age					
Late preterm	1,053.4/14,773.1	7.1	291.1/3,757.9	7.8	.33
Early term	4,250.2/14,773.1	28.8	1,095.6/3,757.9	29.2	
Full term	9,469.5/14,773.1	64.1	2,371.2/3,757.9	63.0	
Neonatal and infant variables					
Neonatal special care					
Yes	1,263.9/14,766.6	8.6	334.3/3,756.8	8.9	.51
No	13,502.7/14,766.6	91.4	3,422.5/3,756.8	91.1	

	Respondents		Non-respondents		
	N	%	N	%	p-value
Breastfeeding					
None	n/a		n/a		
≤6 months					
>6 months					
Social context variables: family structure					
Maternal partnership status					
Single parent family	1,469.1/14,773.1	9.9	518.5/3,757.9	13.8	<.001
Two parent family	13,304.0/14,773.1	90.1	3,239.4.3,757.9	86.2	
Number of siblings					
3 or more	860.9/14,773.1	5.8	224.3/3,757.9	6.0	<.001
1 to 2	7,861.3/14,773.1	53.2	1,870.6/3,757.9	49.8	
None	6,050.9/14,773.1	41.0	1,663.0/3,757.9	44.2	
Social context variables: family resources					
Family income adequacy					
Inadequate	1,995.0/14,773.1	13.5	711.4/3,757.9	18.9	<.001
Adequate	12,778.1/14,773.1	86.5	3,046.5/3,757.9	81.1	
Current maternal education					
Secondary or less	3,689.9/14,469.9	25.5	1,222.1/3,558.1	34.4	<.001
Some post-secondary	3,301.5/14,469.9	22.8	802.6/3,558.1	22.6	
College or university degree	7,478.5/14,469.9	51.7	1,533.4/3,558.1	43.0	
Maternal age (at birth of child)					
<20 years	849.6/14,773.1	5.8	316.5/3,757.9	8.4	<.001
20 years or older	13,923.5/14,773.1	94.2	3,441.4/3,757.9	91.6	
Maternal health					
Poor	510.9/14,441.8	3.5	194.2/3,538.6	5.5	<.001
Good	13,930.9/14,441.8	96.5	3,344.4/3,538.6	94.5	
Maternal mental health					
Depressed	1,375.8/14,093.5	9.8	418.6/3,346.6	12.5	<.001
Not depressed	12,717.7/14,093.5	90.2	2,928.0/3,346.6	87.5	

	Respondents		Non-respondents		
	N	%	N	%	p-value
Social context variables: other					
Family functioning					
Poor functioning	2,371.1/14,134.7	16.8	732.4/3,396.0	21.6	<.001
Not poor	11,763.6/14,134.7	81.2	2,663.6/3,396.0	78.4	
Proximal social processes					
Parenting interactions					
Negative	1,242.7/14,593.9	8.5	329.8/3,674.6	9.0	.37
Positive	13,351.2/14,593.9	91.5	3,344.8/3,674.6	91.0	
Parenting effectiveness					
Ineffective	2,217.8/14,658.6	15.1	604.6/3,694.2	16.4	.06
Effective	12,440.8/14,658.6	84.9	3,089.6/3,649.2	83.6	
Parenting consistency					
Inconsistent	n/a		n/a		
Consistent					
Other covariates					
Child sex					
Male	7,570.8/14,773.1	51.2	1,891.2/3,757.9	50.3	.31
Female	7,202.3/14,773.1	48.8	1,866.7/3,757.9	49.7	

Table B.20. Comparison of Respondents and Non-Respondents at 4-5 Years on Baseline Characteristics (Chapter 4).

	Respondents		Non-respondents		
	N	%	N	%	p-value
Perinatal variables					
Smoking during pregnancy					
Yes	1,993.0/11,588.3	17.2	1,313.6/6,650.2	19.7	<.001
No	9,595.3/11,588.3	82.8	5,336.6/6,650.2	80.3	
Alcohol during pregnancy					
Yes	1,867.8/11,588.3	16.1	948.7/6,637.5	14.3	<.001
No	9,720.5/11,588.3	83.9	5,698.8/6,647.5	85.7	
Placental ischemia and other hypoxia					
Yes	1,440.4/11,589.9	12.4	845.7/6,647.5	12.7	.56
No	10.149.5/11,589.9	87.6	5,801.8/6,647.5	87.3	
Other biological determinants					
Yes	728.0/11,587.4	6.3	408.1/6,648.5	6.1	.69
No	10,859.4/11,587.4	93.7	6,240.4/6,648.5	93.9	
Delivery type					
Caesarean	2,257.6/11,726.6	19.2	1,299.9/6,800.5	19.1	.81
Vaginal	9,469.0/11,726.6	80.8	5,500.6/6,800.5	80.9	
Gestational age					
Gestational age					
Late preterm	836.1/11,729.9	7.1	508.5/6,801.1	7.5	.07
Early term	3,327.0/11,729.9	28.4	2,018.8/6,801.1	29.7	
Full term	7,566.8/11,729.9	63.5	4,273.8/6,801.1	62.8	
Neonatal and infant variables					
Neonatal special care					
Yes	968.1/11,726.7	8.3	630.1/6,796.7	9.3	.02
No	10,758.6/11,726.7	91.7	6,166.6/6,796.7	90.7	

	Respondents		Non-respondents		
	N	%	N	%	p-value
Breastfeeding					
None	n/a		n/a		
≤6 months					
>6 months					
Social context variables: family structure					
Maternal partnership status					
Single parent family	1,060.5/11,729.9	9.0	927.1/6,801.1	13.6	<.001
Two parent family	10,669.4/11,729.9	91.0	5,874.0/6,801.1	86.4	
Number of siblings					
3 or more	609.5/11,729.9	5.2	475.6/6,801.1	7.0	<.001
1 to 2	6,263.4/11,729.9	53.4	3,468.6/6,801.1	51.0	
None	4,857.0/11,729.9	63.4	2,856.9/6,801.1	37.0	
Social context variables: family resources					
Family income adequacy					
Inadequate	1,464.6/11,729.9	12.5	1,241.7/6,801.1	18.3	<.001
Adequate	10,265.3/11,729.9	87.5	5,559.3/6,801.1	81.7	
Current maternal education					
Secondary or less	2,773.3/11,527.0	15.2	2,138.7/6,500.9	32.9	<.001
Some post-secondary	2,618.1/11,527.0	22.7	1,485.9/6,500.9	22.9	
College or university degree	6,135.6/11,527.0	53.1	2,876.3/6,500.9	44.2	
Maternal age (at birth of child)					
<20 years	642.9/11,729.9	5.5	523.3/6,801.1	7.7	<.001
20 years or older	11,087.0/11,729.9	94.5	6,277.8/6,801.1	92.3	
Maternal health					
Poor	399.0/11,509.0	3.5	306.2/6,471.4	4.7	<.001
Good	11,110.0/11,509.0	96.5	6,165.2/6,471.4	95.3	
Maternal mental health					
Depressed	1,026.8/11,238.1	9.1	767.6/6,202.0	12.4	<.001
Not depressed	10,211.3/11,238.1	98.9	5,434.4/6,202.0	87.6	

	Respondents		Non-respondents		
	N	%	N	%	p-value
Social context variables: other					
Family functioning					
Poor functioning	1,830.4/11,272.8	16.3	1,273.0/6,257.9	20.3	<.001
Not poor	9,442.4/11,272.8	83.7	4,984.9/6,257.9	79.7	
Proximal social processes					
Parenting interactions					
Negative	928.9/11,499.4	8.0	643.6/6,669.1	9.7	<.001
Positive	10.670.5/11,499.4	92.0	6,025.5/6,669.1	90.3	
Parenting effectiveness					
Ineffective	1,776.4/11,656.5	15.2	1,046.0/6,696.3	15.6	.49
Effective	9,880.1/11,656.5	84.8	5,650.3/6,696.3	84.4	
Parenting consistency					
Inconsistent	n/a		n/a		
Consistent					
Other covariates					
Child sex					
Male	5,978.7/11,729.9	51.0	3,483.4/6,801.1	51.2	.74
Female	5,751.2/11,729.9	49.0	3,317.7/6,801.1	48.8	

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Appendix C

Thesis Sample Size Calculations

C.1. Thesis Sample Size Calculations Details

Sample size calculations for cohort studies with unequal-sized "exposed" and "unexposed" groups were performed for the primary research questions using the equation described by Kelsey et al. (1). The equation is as follows:

$$n = \frac{\left(Z_{\alpha/2} - Z_{\beta}\right)^2 \bar{p}\,(1-\bar{p})\,(r+1)}{(d^*)^2 r}$$

(Equation C.1)

where:

*d** Is the non-null value of the difference in proportions (i.e., the magnitude of the difference one wishes to detect).

n Is number of exposed individuals to be studied.

r Is the ratio of the number of unexposed individuals studied to the number of exposed individuals studied.

p_1 Is the proportion of exposed individuals who develop (or have) the outcome.

p_0 Is the proportion of unexposed individuals who develop (or have) the outcome.

$\bar{p}$ Is the weighted average of p_1 and p_0: $\bar{p} = \frac{p_1 + rp_0}{1+r}$

RR Is the relative risk, the ratio of p_1 to p_0. (Although not used in the sample size calculation, this value is included in Table C.1 and Table C.2 to provide a more clear representation of the measure of effect to be detected for a given sample size.)

The calculations were carried out for a difference between the late preterm (exposed) and full term (unexposed) groups. The number of individuals needed in the early term group was deduced based on the expected prevalence of late preterm (6%), early term (18%), and full term (74%) births (excluding very preterm births [2%]) based on the literature review (2). Calculations were repeated for each of the outcomes of interest (for Chapter 3, neonatal intensive care unit (**NICU**) triage/admission and neonatal respiratory morbidity; for Chapter 4, developmental delay and receptive vocabulary delay) based on the expected distribution of the outcome in the unexposed group. Sensitivity analyses were performed by varying the magnitude of the difference to be detected between the

unexposed and exposed groups based on a range of plausible differences as described in the literature.

Note that although the sample size calculations were performed for univariable relationships, simple “rules of thumb” can be used to determine whether sample sizes are appropriate for multivariable analyses and interactions. For multivariable analyses, the most commonly cited rule is that there should be 10 outcome observations for every covariate. (Some authors argue that this ratio should be 100:1 (3).) With 22-23 covariates in each of the analyses and common outcomes (prevalence ~10% for each), the actual sample sizes available were more than adequate. For interaction analyses, the needed sample size is usually multiplied by 4 (4). Assuming that minimum relative risks of 2.0 and 1.5 are expected for Chapter 3 and Chapter 4, respectively, both studies were shown to have approximately adequate power to conduct interaction analyses. (Refer to Table C.1 and Table C.2.)

Table C.1. Sample Size Calculations for Chapter 3.

$(Z_{\alpha/2}+Z_{\beta})^2$	p	p_1	p_0	RR (p_1/p_0)	r	d	n (LPT)	n (ET)	n (FT)	Total N	Total N for interaction
NICU triage/admission											
7.849	0.052	0.07	0.05	1.40	12	0.02	1,039.1	3,117.8	12,815.8	16,972.4	67,889.5
7.849	0.052	0.08	0.05	1.60	12	0.03	468.4	1,405.2	5,776.3	7,649.7	30,598.6
7.849	0.053	0.09	0.05	1.80	12	0.04	267.1	801.4	3,294.3	4,362.7	17,450.7
7.849	**0.054**	**0.10**	**0.05**	**2.00**	**12**	**0.05**	**173.3**	**519.9**	**2,137.1**	**2,830.3**	**11,321.1**
7.849	0.055	0.11	0.05	2.20	12	0.06	122.0	365.9	1,504.1	1,991.9	7,967.7
7.849	0.055	0.12	0.05	2.40	12	0.07	90.8	272.4	1,119.7	1,482.9	5,931.4
7.849	0.056	0.13	0.05	2.60	12	0.08	70.4	211.3	868.5	1,150.1	4,600.6
Neonatal respiratory morbidity											
7.849	0.041	0.05	0.04	1.25	12	0.01	3,325.3	9,977.4	41,012.0	54,313.4	217,253.5
7.849	0.042	0.06	0.04	1.50	12	0.02	846.3	2,539.4	10,438.1	13,823.5	55,293.8
7.849	0.042	0.07	0.04	1.75	12	0.03	382.8	1,148.6	4,721.3	6,252.5	25,010.0
7.849	**0.043**	**0.08**	**0.04**	**2.00**	**12**	**0.04**	**219.1**	**657.3**	**2,701.8**	**3,578.1**	**14,312.4**
7.849	0.044	0.09	0.04	2.25	12	0.05	142.6	427.8	1,758.6	2,329.0	9,316.0
7.849	0.045	0.10	0.04	2.50	12	0.06	100.7	302.1	1,241.7	1,644.4	6,577.7
7.849	0.045	0.11	0.04	2.75	12	0.07	75.2	225.6	927.3	1,228.0	4,911.9

(Values for p_1 and p_0 obtained from the literature review.)

Table C.2. Sample Size Calculations for Chapter 4.

$(Z_{\alpha/2}+Z_{\beta})^2$	p	p_1	p_0	RR (p_1/p_0)	r	d	n (LPT)	n (ET)	n (FT)	Total N	Total N for interaction
Developmental delay											
7.849	0.102	0.12	0.10	1.20	12	0.02	1,939.3	5,818.8	23,918.1	31,675.3	126,701.4
7.849	0.102	0.13	0.10	1.30	12	0.03	867.7	2,603.5	10,701.6	14,172.4	56,689.8
7.849	0.103	0.14	0.10	1.40	12	0.04	491.3	1,474.2	6,059.7	8,025.1	32,100.2
7.849	**0.104**	**0.15**	**0.10**	**1.50**	**12**	**0.05**	**316.5**	**949.7**	**3,903.8**	**5,169.9**	**20,679.7**
7.849	0.105	0.16	0.10	1.60	12	0.06	221.3	663.8	2,728.7	3,613.7	14,454.9
7.849	0.105	0.17	0.10	1.70	12	0.07	163.6	490.9	2,017.8	2,672.2	10,688.8
7.849	0.106	0.18	0.10	1.80	12	0.08	126.1	378.3	1,554.8	2,059.1	8,236.3
Receptive vocabulary delay											
7.849	0.203	0.24	0.20	1.20	12	0.04	860.1	2,580.6	10,607.5	14,047.8	56,191.2
7.849	0.205	0.26	0.20	1.30	12	0.06	384.4	1,153.4	4,741.0	6,278.6	25,114.5
7.849	0.206	0.28	0.20	1.40	12	0.08	217.4	652.4	2,681.7	3,551.4	14,205.6
7.849	**0.208**	**0.30**	**0.20**	**1.50**	**12**	**0.10**	**139.9**	**419.8**	**1,725.7**	**2,285.4**	**9,141.7**
7.849	0.209	0.32	0.20	1.60	12	0.12	97.7	293.1	1,205.0	1,595.8	6,383.0
7.849	0.211	0.34	0.20	1.70	12	0.14	72.2	216.5	890.0	1,178.7	4,714.8
7.849	0.212	0.36	0.20	1.80	12	0.16	55.6	166.7	685.1	907.3	3,629.1

(Values for p_1 and p_0 obtained from the literature review.)

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Appendix D

Thesis Ethics Approval Documents

D.1 Ethics Approval

For the *first objective* (Chapters 3) and the *third objective* (Chapter 5), ethics approval was obtained from: (a) the University of Western Ontario Health Sciences Research Ethics Board; and (b) Lawson Health Research Institute Research Office.

For the *second objective* (Chapter 4), access to the Research Data Centres Program was obtained through the Social Sciences and Humanities Research Council. Approval from the University of Western Ontario Health Sciences Research Ethics Board was not needed for this study since this was a secondary analysis of survey data, and individual survey respondents could not be identified.

Research Western

Use of Human Participants - Ethics Approval Notice

Principal Investigator: Dr. Karen Campbell
Review Number: 18770E
Review Level: Delegated
Approved Local Adult Participants: 40000
Approved Local Minor Participants: 0
Protocol Title: Late preterm and early term birth: Is it time to re-define risk groups?
Department & Institution: Epidemiology & Biostatistics, University of Western Ontario
Sponsor: Canadian Institutes of Health Research

Ethics Approval Date: February 16, 2012 **Expiry Date:** February 28, 2017
Documents Reviewed & Approved & Documents Received for Information:

Document Name	Comments	Version Date
UWO Protocol		

This is to notify you that The University of Western Ontario Research Ethics Board for Health Sciences Research Involving Human Subjects (HSREB) which is organized and operates according to the Tri-Council Policy Statement: Ethical Conduct of Research Involving Humans and the Health Canada/ICH Good Clinical Practice Practices: Consolidated Guidelines; and the applicable laws and regulations of Ontario has reviewed and granted approval to the above referenced revision(s) or amendment(s) on the approval date noted above. The membership of this REB also complies with the *membership requirements for REB's as defined in Division 5 of the Food and Drug Regulations.*

The ethics approval for this study shall remain valid until the expiry date noted above assuming timely and acceptable responses to the HSREB's periodic requests for surveillance and monitoring information. If you require an updated approval notice prior to that time you must request it using the UWO Updated Approval Request Form.

Members of the HSREB who are named as investigators in research studies, or declare a conflict of interest, do not participate in discussion related to, nor vote on, such studies when they are presented to the HSREB.

The Chair of the HSREB is Dr. Joseph Gilbert. The UWO HSREB is registered with the U.S. Department of Health & Human Services under the IRB registration number IRB 00000940.

[redacted]

Signature

Ethics Officer to Contact for Further Information

Janice Sutherland [redacted]	Grace Kelly [redacted]	Shantel Walcott [redacted]

This is an official document. Please retain the original in your files.

The **University** *of* **Western Ontario**
Office of Research Ethics
[redacted]

LAWSON HEALTH RESEARCH INSTITUTE

FINAL APPROVAL NOTICE

RESEARCH OFFICE REVIEW NO.: R-12-125

PROJECT TITLE: Late preterm and early term birth: Is it time to re-define risk groups?

PRINCIPAL INVESTIGATOR: Dr. Karen Campbell

DATE OF REVIEW BY CRIC: March 14, 2012

Health Sciences REB#: 18770E

Please be advised that the above project was reviewed by the Clinical Research Impact Committee and the project:

Was Approved

PLEASE INFORM THE APPROPRIATE NURSING UNITS, LABORATORIES, ETC. BEFORE STARTING THIS PROTOCOL. THE RESEARCH OFFICE NUMBER MUST BE USED WHEN COMMUNICATING WITH THESE AREAS.

Dr. David Hill
V.P. Research
Lawson Health Research Institute

All future correspondence concerning this study should include the Research Office Review Number and should be directed to Sherry Paiva, CRIC Liaison, [redacted]

cc: Administration

SSHRC CRSH

[redacted]

July 25, 2012

Ms. Hilary Brown
Department of Epidemiology and Biostatistics
[redacted]

FILE: CISS-RDC-BROWN/566746

Dear Ms. Brown:

Thank you for submitting an application to the CISS-Access to the RDC Program, a joint initiative between Statistics Canada, the Social Sciences and Humanities Research Council and the Canadian Institutes of Health Research. The RDC-Access Granting Committee has now completed the review of your project proposal and has approved it. Before you are granted access to the RDC to begin your project proposal you will need to complete the following steps (http://www.statcan.gc.ca/rdc-cdr/process-eng.htm):

1) Complete the security screening process
2) Sign the Oath of Office and Secrecy
3) Participate in an RDC Orientation session
4) Sign a Microdata Research Contract with Statistics Canada.

Your RDC analyst can be found at the centre listed on the following web page: http://www.statcan.gc.ca/rdc-cdr/network-reseau-eng.htm.

You have 1 year from the date of approval of your project proposal in order to initiate access to the RDC. If you are unable to commence your project proposal within the first 12 months after your project proposal has been approved for RDC access, please contact the RDC analyst to make special arrangements. If you have not contacted your RDC analyst within the first 12 months after your project proposal has been approved, you will need to re-apply to SSHRC in order to re-gain access to the RDC.

The reviews of the project proposal were based on SSHRC peer review procedures. Each project proposal was evaluated on the basis of four main criteria: scientific merit and viability of the proposed research; the viability of the methods to be applied given the data on which the analysis will be performed; a demonstrated need for access to detailed micro data; and, the expertise and ability of the researchers to carry out the work.

Enclosed is a copy of the evaluation results from the SSHRC peer review procedures for your information. If you need to discuss these results please contact your RDC analyst.

SSHRC CRSH [redacted]

Should you have further questions, please feel free to contact the officer responsible for the administration of the CISS-Access to the RDC Program, Mika Oehling, [redacted]

Sincerely,

[redacted]

Éric Bastien
Acting Director
Partnerships Portfolio

cc: Beverley Hunt, Research Data Centres Headquarters Operations

Encl.

Curriculum Vitae

Name	Hilary K. Brown
Post-secondary Degrees	Ph.D., Epidemiology & Biostatistics The University of Western Ontario, 2014 (anticipated)
	M.Sc., Community Health & Epidemiology Queen's University, 2010
	B.A. (Honours), Psychology Queen's University, 2007
Additional Training	Western Certificate in University Teaching and Learning The University of Western Ontario, 2014 (anticipated)
	Summer Institute in Reproductive and Perinatal Epidemiology Canadian Institutes of Health Research and National Institutes of Health, 2012
Scholarships	Postdoctoral Fellowship Canadian Institutes of Health Research, 2014-17
	Postdoctoral Fellowship (declined) Centre for Addiction and Mental Health, 2014-15
	Ontario Graduate Scholarship with Distinction Ontario Ministry of Training, Colleges and Universities, 2013-14
	Frederick Banting and Charles Best Canada Graduate Scholarship Doctoral Research Award Canadian Institutes of Health Research, 2010-13
	Ontario Graduate Scholarship (declined) Ontario Ministry of Training, Colleges and Universities, 2010-11
	Frederick Banting and Charles Best Canada Graduate Scholarship Master's Award Canadian Institutes of Health Research, 2009-10
	Ontario Graduate Scholarship (declined) Ontario Ministry of Training, Colleges and Universities, 2009-10
	Master's Autism Scholars Award (declined) Ontario Council on Graduate Studies, 2009-10

Ontario Graduate Scholarship
Ontario Ministry of Training, Colleges and Universities, 2008-09

Autism Scholars Award
Autism Ontario, 2008-09

Honours and Awards

CIHR National Student Poster Competition Silver Medal
26th Canadian Student Health Research Forum, 2013

Nellie Farthing Fellowship in the Medical Sciences
The University of Western Ontario, 2013

Carol Buck Graduate Scholarship in Epidemiology
The University of Western Ontario, 2011

Dean's Award for Excellence in Research
Queen's University, 2010

Travel Award for Students and Post-Doctoral Fellows
Canadian Institutes of Health Research, 2010

Dean's Honour List with Distinction
Queen's University, 2006, 2007

Special Award for Academic Proficiency
Queen's University, 2006

Related Work Experience

Graduate Teaching Assistant
Department of Epidemiology & Biostatistics
The University of Western Ontario, 2012-14

Research Assistant
Department of Epidemiology & Biostatistics
The University of Western Ontario, 2010-14

Perinatal Database Coordinator
Department of Obstetrics & Gynaecology
The University of Western Ontario, 2012-13

Research Assistant
Department of Community Health & Epidemiology
Queen's University, 2007-10

Publications

Brown HK, Speechley KN, Macnab J, Natale R, Campbell MK. Biological determinants of spontaneous late preterm and early term

birth: A retrospective cohort study. Br J Obstet Gynaecol. (submitted).

Brown HK, Wilk P. Changes in smoking during pregnancy in Ontario women, 1995-2010: Results from the Canadian Community Health Survey. J Obstet Gynaecol Can. (accepted).

Brown HK, Speechley KN, Macnab J, Natale R, Campbell MK. Mild prematurity, proximal social processes, and developmental delay. Pediatrics. (acceepted).

Brown HK, Hill J, Natale R. Caesarean section rates in Southwestern Ontario: Changes across time after adjusting for important medical and social characteristics. J Obstet Gynaecol Can. (accepted).

Brown HK, Speechley KN, Macnab J, Natale R, Campbell MK. Neonatal morbidity associated with late preterm and early term birth: The role of gestational age and biological determinants of preterm birth. Int J Epidemiol. (in press).

Brown HK, Ouellette-Kuntz H, Hunter D, Kelley E, Cobigo V. (2012). Unmet needs of families of school-aged children with an autism spectrum disorder. J Appl Res Intellect Disabil. 2012;25(6):497-508.

Brown HK, Ouellette-Kuntz H, Hunter D, Kelley E, Cobigo V, Lam M. Beyond an autism diagnosis: Children's functional independence and parents' unmet needs. J Autism Dev Disord. 2011;41(10):1291-1302.

Brown HK, Ouellette-Kuntz H, Lysaght, R., & Burge. P. Students' behavioural intentions towards peers with disability. J Appl Res Intellect Disabil. 2011;24(4):322-32.

Brown HK, Ouellette-Kuntz H, Hunter D, Kelley E. Assessing need in school-aged children with an autism spectrum disorder. Res Autism Spectr Disord. 2010;4(4):539-47.

Ouellette-Kuntz H, Brown HK, Baur L, Davis R, Emerson E, Kerr, M, Meijer M, O'Hara D, Proulx R, Perry J, Small J, van Schrojenstein Lantman-de Valk H. Using a knowledge translation lens to develop international collaborations to improve the health of individuals with intellectual disabilities. J Policy Pract Intellect Disabil. 2010;7(4):278-82.

Ouellette-Kuntz H, Burge P, Brown HK, Arsenault E. Public attitudes towards individuals with intellectual disabilities as measured by the concept of social distance. J Appl Res Intellect Disabil. 2010;23(2):132-42.

Brown HK, Ouellette-Kuntz H, Bielska I, Elliott D. Choosing a measure of support need: Implications for research and policy. J Intellect Disabil Res. 2009;53(11):949-54.

Ouellette-Kuntz H, Coo H, Lam M, Yu CT, Breitenbach MM, Hennessey PE, Holden JJA, Brown HK, Noonan AL, Gauthier RB, Crews LR. Age at diagnosis of autism spectrum disorders in four regions of Canada. Can J Public Health, 2009;100(4):268-73.

Jones J, Ouellette-Kuntz H, Vilela T, Brown H. Attitudes of community developmental service agency staff toward issues of inclusion for individuals with intellectual disabilities. J Policy Pract Intellect Disabil. 2008;5(4):219-26.

Presentations

Brown HK, Vigod S, Cobigo V, Lunsky Y. Fertility rates in women with intellectual and developmental disabilities: Methods and preliminary findings from a study in Ontario, Canada. Panel presentation delivered at the 138th American Association on Intellectual and Developmental Disabilities Annual Meeting in Orlando, Florida (June 23-26, 2014).

Brown HK, Speechley KN, Macnab J, Natale, R, Campbell MK. Biological determinants of spontaneous late preterm and early term birth. Oral presentation delivered at the London Health Research Day in London, ON (March 18, 2014); poster presentation delivered at: (1) the 12th Annual Paul Harding Research Awards Day in London, ON (May 15); (2) the 27th Annual Meeting of the Society for Pediatric and Perinatal Epidemiologic Research in Seattle, WA (June 23); and (3) the 47th Annual Society for Epidemiologic Research Meeting in Seattle, WA (June 24-27).

Brown HK, Speechley KN, Macnab J, Natale, R, Campbell MK. Receptive vocabulary delay among children born late preterm and early term: Are risks modified by parenting practices? Poster presentation delivered at the Paediatrics Research Day in London, ON (May 21).

Brown HK, Hill J, Natale R. Caesarean section rates in Southwestern Ontario: Changes across time after adjusting for important medical and social characteristics. Oral presentation

delivered at the 12th Annual Paul Harding Research Awards Day in London, ON (May 14);

Ruttinger S, Brown H, deVrijer B, Richardson BS. Maternal body mass index (BMI) impacts fetal-placental size at birth and umbilical cord PO2 values: Implications for regulatory mechanisms. Oral presentation delivered at the Canadian National Perinatal Research Meeting in Banff, AB (February 12-15, 2014); Poster presentation delivered at the Society for Gynecologic Investigation 61st Annual Scientific Meeting in Florence, Italy (March 26-29, 2014).

Brown HK, Speechley KN, Macnab J, Natale, R, Campbell MK. Developmental delay at 2-3 years: Relative importance of gestational age and social risk factors. Oral presentation delivered at (1) the London Health Research Day in London, ON (March 20, 2013); and (2) the Canadian Society for Epidemiology & Biostatistics Biennial Conference in St. John's, NL (June 25-27, 2013). Poster presentation delivered at (1) the 26th Canadian Student Health Research Forum in Winnipeg, MB (June 4-6, 2013) and (2) the European Congress of Epidemiology in Aarhus, Denmark (August 11-14, 2013).

Clarson C, Brown H, DeJesus S, Jackman M, Mahmud F, Prapavessis H, Shoemaker K, Wilson J, Hill D. Sustained reduction of BMI z score with Metformin extended release and structured lifestyle intervention in obese adolescents. Poster session presented at the American Diabetes Association 73rd Scientific Sessions in Chicago, IL (June 21-25, 2013).

Brown HK, Speechley KN, Macnab J, Natale, R, Campbell MK. The association between late preterm and early term birth and neonatal intensive care unit triage/admission: Role of the biological determinants of early delivery. Poster presentation delivered at (1) the 26th Annual Meeting of the Society for Pediatric and Perinatal Epidemiologic Research in Boston, MA (June 17-18, 2013) and (2) the 46th Annual Society for Epidemiologic Research Meeting in Boston, MA (June 18-21, 2013).

Brown HK, Speechley KS, Macnab J, Natale, R, Campbell MK. Neonatal respiratory morbidity: Roles of mild prematurity and biological determinants of preterm birth. Oral presentation delivered at the 11th Annual Paul Harding Research Awards Day in London, ON (May 11, 2013).

Brown HK, Speechley KN, Macnab J, Natale, R Campbell MK. Outcomes of late preterm and early term birth: Developing conceptual models to inform hypotheses. Poster presentation delivered at the London Health Research Day in London, ON (March 20, 2012).

Brown HK, Campbell MK. Neonatal and childhood outcomes of late preterm and early term birth: A conceptual framework. Poster presentation delivered at the Canadian Society for Epidemiology & Biostatistics National Student Conference in Montréal, QC (June 19-20, 2011).

Brown HK, Ouellette-Kuntz H, Hunter D, Kelley E. Characteristics associated with unmet need in families of school-aged children with an autism spectrum disorder. Oral presentation delivered at the Canadian Society for Epidemiology & Biostatistics Student Conference in Kingston, ON (May 27-28, 2010).

Brown HK, Ouellette-Kuntz H, Hunter D, Kelley E. An examination of the support needs experienced by families of school-aged children with an autism spectrum disorder. Oral presentation delivered at the International Meeting for Autism Research in Philadelphia, PA (May 20-22, 2010).

Brown HK, Ouellette-Kuntz H, Hunter D, Kelley E. An examination of the support needs experienced by families of school-aged children with an autism spectrum disorder. Poster presentation delivered at (1) the Canadian Association for Health Services and Policy Research Conference in Toronto, ON (May 10-13, 2010) and (2) the Queen's University 13th Annual Scientific Meeting for Health Sciences Research Trainees in Kingston, ON (June 1, 2010).

Coo H, Brown H, Ouellette-Kuntz H, Lam M, Yu CT, Lewis MES, Dewey D, Bernier F, Chudley AE, Breitenbach M, Noonan AL, Hennessey P, Crews LR, Holden JJA. Age at first diagnosis of an autism spectrum disorder in four regions of Canada. Poster presentation delivered at: (1) the International Meeting for Autism Research in Chicago, IL (May 7-9, 2009); (2) the Canadian Society for Epidemiology & Biostatistics National Student Conference in Ottawa, ON (May 24, 2009); and (3) the Queen's University 12th Annual Scientific Meeting for Health Sciences Research Trainees in Kingston, ON (June 2, 2009).

Ouellette-Kuntz H, Elliott D, McDonald M, Koven R, Brown H, Bielska IA. Adults with intellectual disabilities and psychiatric or

behavioural co-morbidity: Understanding the needs of a subpopulation to enhance service planning. Poster presentation delivered at: (1) Central Region Community Network of Specialized Care Research Workshop in Toronto, Ontario (April 30, 2008); (2) the 19th Biennial Canadian Society for Epidemiology and Biostatistics Research Central Region Student Conference in St. Catherines, Ontario (May 29, 2008); and (3) the Queen's University 11th Annual Scientific Meeting for Health Sciences Research Trainees in Kingston, ON (June 1, 2008).

Arboleda-Flórez J, Stuart H, Brown H. Advocacy through theatre. Oral presentation delivered at the Third International Stigma Conference: Together Against Stigma in Istanbul, Turkey (October 5-8, 2006).

Invited Presentations

Brown HK. Unmet needs of school-aged children. Oral presentation delivered at the National Epidemiological Database for the Study of Autism in Canada Knowledge Transfer Event in Kingston, ON (March 21, 2012).

Zhu L, Brown HK, Goodwin S, Campbell MK. Fetal environment and adult disease: a life-course perspective. Group oral presentation delivered at: (1) The University of Western Ontario Department of Epidemiology and Biostatistics Seminar Series in London, ON (December 9, 2011) and (2) The University of Western Ontario Department of Physiology and Pharmacology Seminar Series in London, ON (January 18, 2012).

Brown HK. Trends in active and passive smoking during pregnancy in Ontario, 2001-2007. Oral presentation delivered at the Middlesex-London Health Unit in London, ON (April 6, 2011).

Brown HK, Ouellette-Kuntz H, Hunter D, Kelley E. An examination of the support needs experienced by families of school-aged children with an autism spectrum disorder. Oral presentation delivered at the Autism Spectrum Disorders—Canadian-American Research Consortium June Trainees Videoconference in Kingston, ON (June 16, 2010).

Brown HK, Ouellette-Kuntz H, McDonald M. Whaddaya think? Students' behavioural intentions towards peers with disability. Oral presentation delivered to the South Eastern Ontario Community-University Research Alliance in Intellectual Disabilities Community Living North Grenville Consumer Advisory Group in Kemptville, ON (June 9, 2010).

Academic Service

Judge
Canadian Society for Epidemiology and Biostatistics Student Conference, 2014

Abstract Reviewer
Society for Epidemiologic Research, Society for Perinatal and Pediatric Research, Canadian Society for Epidemiology and Biostatistics, 2014

Scholarship Reviewer
National Scholarship Program
The University of Western Ontario, 2013-present

Academic Program Student Reviewer
School of Graduate and Postdoctoral Studies
The University of Western Ontario, 2013

Schulich Graduate Studies Student Representative
Schulich School of Medicine & Dentistry
The University of Western Ontario, 2012-present

Peer Mentor
Department of Epidemiology and Biostatistics
The University of Western Ontario, 2012-present

Department Student Representative
Department of Epidemiology and Biostatistics
The University of Western Ontario, 2012-13

Student Consultant
"Consult the Experts" sessions on Tri-Council funding applications
The University of Western Ontario, 2012

Member
Planning Committee for the London Health Research Day
The University of Western Ontario, 2011-12

Member
Planning Committee for Margaret P. Moffat Research Day
The University of Western Ontario, 2010-11

Co-Chair, Communications
Planning Committee for National Student Conference
Canadian Society for Epidemiology and Biostatistics, 2009-2010

Journal Article Reviewer
Journal of Applied Research in Intellectual Disabilities, Journal of Intellectual Disability Research, Journal of Policy and Practice in Intellectual Disabilities, 2008-present

Professional Affiliations

International Epidemiological Association, 2012-present

Society for Paediatric and Perinatal Epidemiologic Research, 2012-present

Society for Epidemiologic Research, 2012-present

Canadian Society for Epidemiology and Biostatistics, 2010-present