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Predicting Respiratory Disorders in Term and Late Preterm Infants

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Abstract

A population-based retrospective cohort generated by linking Obstetric and NICU databases at St Joseph's Health Care was used to generate a tool capable of predicting respiratory disorders in term and late preterm infants. Singletons were included, while multiples, congenital anomalies, and infants that were small (<3 percentile) and large (>97 percentile) for gestational age were excluded from analyses. Descriptive statistics and risk ratios were used to compare morbidity rates, intervention use and NICU admission rates. Multivariable logistic regression was used to construct the predictive model. Morbidity rates, intervention use and NICU admission rates decreased with increasing gestational age. Little difference was apparent in discrimination and calibration across the ten models constructed and thus model 10 which uses 1/3 of the predictors while maintaining better than good discrimination and calibration may be the most clinically applicable. Ultimately, this tool may assist clinicians in differentiating high from low risk infants who may appear healthy or stable at birth.

Keywords: Late preterm, respiratory distress syndrome, transient tachypnea of the newborn, predictive model

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List of Tables

List of Figures

List of Appendices

Chapter 1: Literature Review

1. 1 Problem Statement

A sharp contrast in mortality rates has been reported between late preterm and term infants. Among late preterm infants, the neonatal mortality rate (deaths among infants between 0 to 27 days) was four fold greater (4.8 versus 1.2 deaths per 1000 live births) than mortality rates in term infants and has remained relatively constant between 1995 and 2002.[115,78] Even greater differences are apparent when considering short and long term morbidity. Kinney et al[98] found that an infant's brain at 34 weeks gestation is only 2/3 of the volume of a term infant while other authors have noted that late preterm infants have less developed gastrointestinal, immune and respiratory systems than term infants. [87] These differences in developmental maturity are believed to contribute to important differences in morbidity rates. More specifically, late preterm infants have been observed to develop hypothermia about 10 times more frequently, respiratory distress about 7 times more frequently, apnea approximately 4 times more frequently, and hypoglycemia and poor feeding about 3 times more frequently than term infants.[181]Furthermore, studies conducted in the United States indicate that late preterm infants have longer neonatal intensive care unit(NICU) stays[49], and higher rates of re-hospitalization both postnatally following initial discharge [28] and later into infancy. [48] As a result, the care of late preterm infants has been observed to incur greater health care costs. [47]

1.1.2 Canadian Institute for Health Information Data on NICU Costs in Canada

CIHI data indicate that 13.6% of newborns (excluding Quebec and Manitoba) were admitted to the NICU in 2003-2004 compared to 12.6% in 1994-1995. The average NICU cost per baby in 2002-2003 was $9700, representing 4% of total hospital costs for the 27 hospitals providing data [24]. Interventions believed to lead to higher costs associated with NICU versus other neonatal care include respirators, monitors, intravenous pumps, kidney dialysis equipment, health personnel, surfactant, radiological investigations, blood-product transfusions, surgery and echocardiography

[139, 108,91]. In addition to hospital costs for NICU treatment, $12 million was billed by fee-for-service physicians in Canada for neonatal intensive care services in 2002-2003. [24] This figure does not include physician billing through alternative payment plans. Total expenditures on preterm birth were not reported by CIHI.

1.1.1 NICU Costs in the United States of America

Preterm birth places a significant strain on health care resources in the United States of America, requiring more than $2 billion per year to prevent or treat complications associated with preterm birth. Although infant mortality rates have dropped as a result of the development of NICUs, significant short and long term morbidity are important potential consequences of preterm birth. Gilbert et al[62] found that overall morbidity rates, intervention use, lengths of stay and costs per infant decreased with increasing gestational age. Interestingly due to greater numbers of infants with each week increase in gestational age, total costs for each week of gestation were nearly constant between 25 and 36 weeks gestation. In the same study, Gilbert estimated that avoiding non-medically indicated births between 34 and 37 weeks could have saved the State of California alone an estimated $50 million USD.

1.1.4 Long-Term Outcomes

As evidenced above, short term outcomes have been studied in some detail. Long term outcomes however, have not been investigated to the same extent. One study observed that infants of moderately low birth weight (1500g to 2500g), the range which many late preterm infants fall within, are more likely to develop special health care needs, chronic conditions and learning disabilities. A number of studies comparing late preterm infants with term infants indicate a greater risk of a variety of long term morbidities including cerebral palsy[177], speech language pathologies [78,133], and neurodevelopmental impairment. [2] These infants are also susceptible to behavioral disorders (including attention deficit disorder) [37], social problems [117] and academic issues.[80] Most recently a study on school aged children found that late preterm infants scored lower on both math evaluations between Kindergarten and

grade one and reading evaluations between Kindergarten and grade five. Furthermore, late preterm infants required special education more frequently than term infants.

1.1.5 Societal Implications and Significance

Given that late preterm births account for the majority of preterm births (74.1% of all preterm births in 2002), [40] even small increases in the rate of late preterm birth could have sizable public health implications[144]. In an effort to advocate for earlier interventions aimed at limiting short and long term morbidity and to provide support for emerging therapies that prevent preterm birth, this study will focus on quantifying the problem of preterm birth from a clinical standpoint. From a clinical perspective, clinicians have an obligation to provide the best possible care for each infant as the consequences of their care have implications that span entire life times. Accordingly, this study will aim to improve evidence based practice in the short term by assisting health care providers in improving the monitoring and treatment of late preterm infants immediately following birth. As well, this study may be used to help guide non-emergency obstetric intervention decisions and improve knowledge of maternal care. It may also be useful to health care planning committees in forecasting future health care budgets. In the long run, earlier interventions could prevent long-term morbidities and as a secondary societal benefit, early intervention could also limit health, education and social service spending. With these considerations in mind, this study will focus on developing a tool that can aid clinicians in predicting which infants will develop respiratory disorders.

1.2 Literature Review/Search Strategy

A literature search conducted between May 1st 2007 and April 30th 2008 employed Pubmed, Medline, Google Scholar, Web of Science, and EMBASE. The goal of the search was to capture all published literature relating to late preterm infants. A pilot review of the literature indicated that a great deal of the most recent literature was in review form, thus the search strategy included extensive searching of cited references. To ensure all potential studies were captured, guidance was provided by an experienced librarian at the University of Western Ontario.

Inclusion Criteria

Broad inclusion criteria were applied to achieve the previously stated goal of capturing the available literature in its entirety. A two phase approach was conducted. Initially, articles which met the following inclusion criteria were reviewed; studies conducted on humans, published in English and containing the following keywords; late-preterm, near-term, moderately premature, moderately preterm, mild premature/preterm, marginally preterm/premature. These keywords were searched individually and in combination with neonat*, bab*/baby/babies, newborn and infant.

Following collection of studies meeting the first set of inclusion criteria, articles were excluded based on relevance and methodological quality. Studies were excluded if there was no attempt by the authors to explain developmental immaturity, quantify mortality or morbidity or review the available research on late preterm infants. For example a number of studies were excluded because the authors attempted to validate new methods of hyperbilirubinemia screening, while others were excluded because the focus was on testing a therapeutic intervention. Accordingly, such studies were deemed outside the scope of this manuscript.

1.3 Late Preterm Birth Defined

Defining "late preterm" is complicated by the use of statistical and conventional medical definitions of gestation in the literature [47]. The first day of the mother's last menstrual period is counted as day 0 when using the statistical definition and day 1 when using the conventional medical definition [46]. The use of "completed weeks" is also worth clarifying. Completed weeks of gestation are defined as the number of 7-day intervals after the first day of the last menstrual period [48, 136]. Using an example to clarify any potential confusion; 36 6/7 weeks' gestation is by definition the end of the 36th completed week of gestation since 36 seven-day intervals have been completed.

Furthermore it is important to note that 37 6/7 weeks' gestation is the 37th completed week, and the following day is the beginning of the 38th week (38 0/7 weeks' gestation). [134]

With this terminology in mind, The American Academy of Pediatrics[4], the American College of Obstetricians and Gynecologists, and the World Health Organization define "preterm birth" as a birth that occurs before 37 completed weeks after the onset of the mother's last menstrual period[174]. This equates to 259 days or earlier in common medical terminology and to 258 days by the statistical definition. Term birth includes delivery between the first day of the 37th week to the last day of the 42nd week (Days 260 to 294), while post term birth includes any birth on or following the 43rd week (295th day) following the start of the last menstrual period.

Infants born preterm between 34 and 36 weeks' gestation represent a potentially underappreciated and understudied group.[9] Infants born during this time period have been classified in the literature by a variety of names including near-term,[167] moderately premature,[103]marginally preterm, minimally preterm, mildly preterm[112] and most recently late preterm[134]. A quick review of the literature illustrates that variation exists even within the definition of near-term as for example, near-term has been defined as both 34 to 36 weeks' gestation[134] and 35 to 36 6/7 weeks' gestation[167]. A common or conventional definition could be helpful in improving retrieval of information on infants born between 34 to 36 weeks' gestation, which in turn could assist in improving epidemiologic, health services research and ultimately clinical practice [134].

In an effort to realize these potential benefits, a consensus definition for infants born between 34 to 36 weeks has been developed by the National Institute of Child Health and Human Development Sponsored Panel on Optimizing Care and Outcomes for Late Preterm (Near-Term)Infants. The Panel defined infants born between 34 and 0/7 days through 36 and 6/7 days (day 239-259) starting from the initial day of the mother's last menstrual period as late preterm infants (LPI) .[46] The panel stated that

the use of "near-term" should be abandoned as it may give the misleading impression that these infants are almost term. This impression may in turn lead to underestimation of risk resulting in less stringent monitoring, evaluation and follow up which in turn could lead to greater morbidity and mortality in the late preterm population.[118]

The panel concedes that the definition is imperfect due to the somewhat arbitrary nature of the 34 week cutoff. However, according to the panel, a lower limit of 34 weeks is justified for a number of reasons. It was argued that 34 weeks is a milestone for maturation of the fetus in obstetrical practice [37] and it is also a cut off point for obstetricians deciding patient care. More specifically 34 weeks is the point at which tocolytics and steroids are generally discontinued, as well it is the point at which mothers with premature rupture of membrane are often induced [134]. Thirty-four weeks also represents a dividing point presently used in health services and epidemiologic research and has been identified as a period in which NICU admission rates tends to vary. Variation in NICU admission is evidenced by a study in which almost all infants born before 33 weeks'gestation are admitted to the NICU, however only 44-88% of infants born at or beyond 34 weeks are admitted. [144]

As mentioned the definition of infants born between 34 to 36 weeks varies, as some studies analyzed infants born between 35 to 36 weeks' gestation. For the purposes of this manuscript, where studies were not conducted on infants born between 34 to 36 weeks' gestation, explicit explanation of the study sample will be provided. Otherwise, for the above justifications, "late preterm" will be used instead of near-term (or other terminology) when describing infants born between 34 to 36 weeks' gestation.

1.4 Epidemiology and Trends Associated with Late Preterm Birth

Despite, and potentially a consequence of advances in obstetrical care, the preterm birth rate continues to rise in the United States [113]. Between 1981 and 2003, the

preterm birth rate rose from 9.4% to 12.3% [113]. This trend illustrates a consistent divergence from the US government's goal of reducing the preterm birth rate to 7.6% as part of the Healthy People 2010 Initiative.[40] Continued divergence is evident in the gestational age distribution, which appears to be shifting according to data from the US National Center for Health Statistics. In analyzing the data from approximately 3 million singleton births per year between 1992 and 2002, investigators from the March of Dimes found that the mean gestational age for spontaneous births in the United States dropped from 39.2 to 38.9 weeks' gestation ($P<0.001$). In the same study, the most common gestational age of singleton babies born in the United States dropped from 40 to 39 weeks' gestation. This left shift is associated with an increase in the late preterm birth rate.[40]

The changing distribution was hypothesized to be a consequence of a large increase in the proportion of births between 34 to 39 weeks, accompanied by a large decrease in singleton births between 40 to 44 weeks gestation. Upon further inspection, it was evident that the proportion of births between 42 to 44 weeks dropped by 31.5%, while births between 37 and 39 weeks' gestation increased by 19.4%. This trend towards earlier births is not likely explained by a rise in infants born before 32 weeks' gestation as the rate of births before 32 weeks' has remained relatively steady at 1.8% to 2.0% during this same time period.[40] By comparison, Kramer et al[98] estimated both the late preterm birth rate and the infant mortality rate using a population-based cohort study. For the US birth cohorts, late preterm infants accounted for 6.3% and 7.6% of all births for 1985 and 1995 respectively. The late preterm birth rate for the Canadian birth cohorts were 4.5% and 4.9% for 1985 to 1987 and 1992 to 1994 respectively, indicating a relatively stable late preterm birth rate in Canada.

With these trends in mind, careful examination of late preterm birth rates may help explain the aforementioned trends. While the proportion of infants born preterm has increased by 30% between 1981 and 2003, the proportion of late preterm births has increased by 40% (6.6% to 8.8%).[113] Similar trends were observed in a study by Martin et al in which the proportion of late preterm births rose from 7.3% to 9.1%

between 1990 to 2005. [113] Thus, the late preterm birth rate is increasing at a faster rate than the overall preterm birth rate (9.4% to 12.3% 30% increase versus 6.3% to 8.8% 40% increase). Furthermore, late preterm infants account for the greatest proportion (71.3%) of preterm births. Accordingly, late preterm births are believed to be responsible for the majority of the rise in the preterm birth rate. [134]

A number of hypotheses have been generated in an attempt to explain the rise in late preterm birth. One theory posits that the rise may be a consequence of more multifetal pregnancies stemming from greater use of reproductive technologies. [70, 106,107, 121, 151, 152] A number of studies support the hypothesis that the most likely explanation for the rise in the number of Late Preterm Infants was due to a combination of greater fetal surveillance and more medical interventions in pregnancies at or beyond 34 weeks' gestation. In support of this hypothesis, an association between greater fetal monitoring (68.1% to 85.4% for electronic fetal monitoring and 47.6% to 67% for ultrasonography) and a rise in late preterm birth rates has been observed between 1989 and 2003. [40, 70, 152, 121, 109] As an example, more women may deliver between 34 to 36 weeks because infants at risk of stillbirth may be identified earlier through more stringent fetal monitoring. [113] Thus, Davidoff et al.[40] concluded that greater use of cesarean sections at early gestations, combined with greater use of induction at later gestations, may help explain the trend toward shorter pregnancies.

1.5 All Cause Mortality from National-Level Population-Based Studies

In a population-based study of US and Canadian preterm infants, mortality rates in Canada(excluding Ontario) and in the United States for infants born between 32 to 36 weeks of gestation were compared to infants born at 37 or more weeks of gestation. The Risk Ratio of mortality for infants born between 34 and 36 weeks was 2.9 (95% CI, 2.8-3.0) in Canada, while the Risk Ratio was higher in the United States, 4.5 (95% CI, 4.0-5.0). [101]

Using US period-linked infant mortality data from 50 States and the District of Columbia between 1995 to 2002, Tomashek et al[163] assessed 187 830 singleton death

records. From this sample, 18 484(9.8%) were late preterm infants and 67 197 (35.8%) were term infants. Infant mortality decreased among late preterm infants by 16.8%, p<0.01) and by 20.0% p<0.01) among term infants during this period. Overall however, late preterm infant mortality rates remained relatively constant between 1995 to 2002 at about three fold higher than overall infant mortality rates in term infants. Two-thirds of all deaths in late preterm infants were accounted for by congenital malformations, sudden infant death syndrome, accidents, diseases of the circulatory system and intrauterine hypoxia and birth asphyxia. [163]

1.6 DEVELOPMENTAL IMMATURITY AND CLINICAL OUTCOMES

1.6.1 Morbidity Associated with Late Preterm Birth

Because late preterm infants may be similar in size[167] to term infants and appear healthy or stable at birth, late preterm infants may be mistakenly cared for by parents[9,171] and health care providers as if they are term infants. [53] Further complicating this issue is the observation that late preterm infants are frequently cared for either by health care providers in Level 1 nurseries or by their mother. [134] However, according to numerous studies, late preterm infants are less physiologically, immunologically and metabolically mature as compared to term infants. [134] As a consequence of this developmental immaturity, late preterm infants are believed to be at a greater risk than term infants, of a variety of morbidities including respiratory distress, hypoglycemia, hypothermia, and hyperbilirubinemia during the birth hospitalization. In addition, late preterm infants may be at an increased risk of retinopathy of prematurity, apnea, feeding problems, bronchopulmonary dysplasia, intraventricular hemorrhage, periventricular leukomalacia, necrotizing enterocolits and infection. Late preterm infants are also more likely to be admitted to the NICU, to be rehospitalized, to develop long term neurodevelopmental problems and to ultimately incur greater health costs than term infants. [167, 49, 127, 135, 102, 149, 163] The following will summarize and assess the available literature with respect to developmental immaturity and its relation to the aforementioned clinical outcomes.

1.6.1.1 Short Term Neurological Outcomes

The literature related to the incidence of neurological morbidities in late preterm infants is limited and is mainly available for infants born earlier at lower birthweights. For example, the incidence of periventricular leukomalacia has been approximated at 3 to 4% in infants of birth weight greater than 1500g. Clinical factors associated with PVL include chorioamnionitis, prolonged rupture of membranes, asphyxia, sepsis, and hypocarbia. Infants affected by PVL typically have long term neurodevelopmental deficits related to motor, cognitive and visual functioning. The incidence of Periventricular-intraventricular hemorrhage lesions has been estimated at approximately 10 to 15% in infants of birth weight greater than 1000g. Long-term motor and cognitive functioning may be poor among all infants affected by this lesion. Periventricluar leukomalacia is hypothesized to be a leading cause of cerebral palsy, and the incidence of PVL may be greater in mothers with chorioamnionitis. A meta-analysis by Wu et al [177] concluded that chorioamnionitis is a risk factor for cystic PVL and cerebral palsy. Significant risk factors associated with development of cystic periventricular leukomalacia according to study by Resch and co-workers[139], were premature rupture of membranes (OR=4.67), chorioamnionitis(OR=6.03), and hyperbilirubinemia (OR=2.46). These results support the potentially causal role of intrauterine infection in periventricular leukomalacia. In Clark's prospectively collected cohort study of 1011 infants who were born at greater than 34 weeks' gestation and intubated within 72 hours of birth (and expected to be ventilated for more than 6 hours) intraventricular hemorrhage was observed in 86 infants with varying severities (grades 1 to 2, n=29; grades 3 to 4, n=6). In assessing risk factors for adverse neurological events using multivariable regression, Clark found a major neurological anomaly or a primary diagnosis of hypoxic–ischemic encephalopathy (adjusted OR=18.5, CI=8.4 to 42.2, p<0.001); treatment with extracorporeal membrane oxygenation (adjusted OR=3.6, CI=1.5 to 8, p=0.002); treatment with vasopressors (adjusted OR=3.2, CI=1.8 to 5.6, p<0.001); and an Apgar score less than 5 at 5 minutes (adjusted OR=2.6, CI=1.3 to 4.8, p=0.004) were associated with a greater risk of adverse neurological event.

1.6.1.2 Long Term Neurodevelopmental Outcome

Long term outcomes have not been investigated to the same extent. . One study observed that infants of moderately low birth weight (1500g to 2500g), the range which many late preterm infants fall within, are more likely to develop special health care needs, chronic conditions and learning disabilities. A number of studies comparing late preterm infants with term infants indicate a greater risk of a variety of long term morbidities including cerebral palsy[177], speech language pathologies [78,133], and neurodevelopmental impairment. [2] These infants are also susceptible to behavioral disorders (including attention deficit disorder) [37], social problems [117] and academic issues.[80] Most recently a study on school aged children found that late preterm infants scored lower on both math evaluations between Kindergarten and grade one and reading evaluations between Kindergarten and grade five. Furthermore, late preterm infants required special education more frequently than term infants.

1.6.2 Nervous System Development

1.6.2.1 Gray Matter Development in the Late Preterm Brain

Rapid development of the central nervous system occurs after 20 weeks gestation. During this time, the weight of the fetal brain increases by 90% in a nearly linear fashion. [66] The fetal brain grows at 15 mL per week between 29 to 41 gestational weeks. [81] Between 28 and 34 weeks the brain grows from 13% to 65% [66]of the weight of a term infant. Accordingly, an infant born at 34 weeks has achieved slightly less than 2/3 of the maturation that is achieved over the final 3 to 8 weeks leading to term birth. Numerous studies have observed that the fetal brain develops in a sort of hierarchical manner. More specifically a number of studies have observed brain development proceeds caudally to rostrally, ie rhomboencehphalon precedes the diencephalon followed by the telencephalon. Central nervous system myelination appears to also proceed in a hierarchical manner in which the primary cortex develops

before the association cortical regions. Furthermore the brain stem and thamalus which are responsible for cerebral cortical relay, exhibit earlier dendritic development than the cerebral cortical areas which are associated with higher cognitive functioning. [166, 123] Subplate neurons achieve their highest density between 22 and 34 gestational weeks.[60]After 34 weeks, pruning via programmed cell death takes place for six months postnatally, altering the neurochemical make up of the developing brain. [100]

Also after 34 weeks, the volume of white matter, largely responsible for facilitating communication among the various regions of the brain, increases in mass more than five fold. [81] During this time period substantial structural maturation has been documented including greater neuronal connectivity, dendritic arborization and connectivity; increasing numbers of synaptic junctions; as well as maturation of neurochemical and enzymatic processes which contribute to growth and maturation of the brain. [97] Different gray and white matter regions of the fetal brain develop at different rates and temporalities. For example, the subplate neurons which are the first neurons to differentiate in the ventricular region of the cerebral cortex [102], play an important role in establishing correct neuronal wiring [60], as well as ensuring maturation of cognitive and motor functioning. [82] Late preterm infants must undergo these neurodevelopmental processes in a comparatively harsh extra-uterine environment, potentially making the late preterm infant more vulnerable to white and/or gray matter injury. [19] Likewise damage to subplate neurons may have severe consequences in the late preterm infant, resulting potentially in cognitive deficits. More specifically, damage to the central nervous system can result in a variety of neurological morbidities in the late preterm infant including periventricular leukomalacia, hypoxic ischemia, and intraventricular or intracranial hemorrhage, potentially resulting in long term auditory, visual or cognitive deficits.

Periventricular leukomalacia (PVL) may present histopathologically as either focal necrotic lesions which are correlated with cerebral palsy and as diffuse white matter lesions which are correlated with cognitive and behavioral problems.[166] The incidence

of PVL in the late preterm infant is presently unknown, but is believed to be rare. PVL is thought to be a consequence of infection that compromises the fetus. [97] The compromised fetus is in turn susceptible to normally benign pre-oligodendrocyte insults resulting from hypoxia ischemia, which harm the vulnerable infant. Late preterm infants may exhibit low oxygen circulation, termed hypoxic ischemia. Hypoxic ischemia encompasses two pathways leading to oxygen deficiency, diminished oxygen supply in the blood (hypoxic) and decreased blood perfusing brain tissue (ischemia). Neuronal cell injury and death are primarily a consequence of low plasma concentrations of glucose and oxygen, two major molecules from which the brain derives energy. Neuronal energy can be used quickly and cell death can follow because neither glucose nor oxygen is stored in the brain. [166] Thus, infection and hypoxia ischemia may synergistically harm the infant, when neither alone would inflict damage necessary to cause brain damage via periventricular leukomalacia. [97]

To protect against neurological insult resulting from oxygen free radicals, the body normally defends itself via antioxidant systems which are both enzymatic (catalases, peroxidases, dismutases) and non-enzymatic (glutathione, cholesterol, ascorbic acid, tocopherol). [42] However, a late preterm infant may not be able to defend him or herself against hypoxia ischemia due to developmental immaturity of these protective mechanisms. Areas which lag in production of these protective mechanisms may suffer preferentially.[19] For example, neuronal immunostaining for catalase, an enzyme essential in reducing hydrogen peroxide, is believed to be present at 27 to 28 weeks in the thalamus, basal ganglia and cerebellum, but is absent from the frontal cortex until the 35th week. These disparities may explain why gray matter areas in this region suffer particularly before 35 weeks. [79] Likewise, a number of studies have reported damage to cerebral areas which appear to correlate with gestational or postnatal age, ie certain areas of the brain may be more prone to injury at different stages of development. Hypoxia ischemic insults may be especially harmful to white matter regions in the preterm infant, however after a few months postnatally, similar insults are observed to harm gray matter regions [19, 7].

1.6.3 Thermoregulation

A number of factors predispose late preterm infants to cold stress and may subsequently lead to a greater risk of hypothermia. An infant's ability to respond to cold stress or thermoregulate, is believed to be a function of gestational age, physical size, brown and white adipose tissue concentrations, as well as maturity of the hypothalamus. Infants born at term achieve higher levels of brown adipose tissue accumulation and maturation. Additonally enzyme levels related to brown fat metabolism are higher in term infants. All newborns regardless of gestational length may be at risk of cold stress at birth unless protective measures are in place. [113] Few studies have attempted to determine the incidence of hypothermia in late preterm infants. Comparisons have been made to term infants in a limited number of studies. In Wang et al's study for example, infants born between 35 to 36 6/7 weeks' gestation experienced greater rates of temperature instability (10% vs 0%; OR: infinite; P = 0.012 using Fisher's exact test) than infants born between 37 to 40 weeks' gestation. In a study by Seubert et al[147] which included infants born late preterm, of 553 infants born between 32 and 36 weeks' gestation at a tertiary care hospital there was significantly greater incidence of hypothermia before 35 weeks ($p<0.001$).

1.6.4 Gastrointestinal Maturation and Feeding Issues

1.6.4.1 Gastrointestinal Issues

The developmental immaturities observed in late preterm gastrointestinal tracts provide an interesting departure from previously observed trends in late preterm developmental immaturity. Despite a doubling in length of the Gastrointestinal Tract in the last trimester, combined with a greater increase in surface area arising from the growth of villus and microvillus, the developmental immaturity of the late preterm infant's gastrointestinal absorptive functioning does not appear to limit digestion of protein, lipids or carbohydrates[83]. Hyman et al reported[83] that despite decreased gastric acid secretion and decreased enterokinase activation of pancreatic proteases limiting the protease cascade, late preterm infants were capable of tolerating whole

protein formulas. Similarly, it may be expected that lipid digestion may be limited in late preterm infants because of decreased bile acid secretion and lower reabsorption in the ileum. A meta analysis conducted by Klenoff-Brumberg and Genen[94] however reported no evidence of a difference in weight gain when comparing median and long chain fatty acid digestion, indicating that late preterm infants can adapt their metabolism to either diet. Similar findings were observed with respect to carbohydrate digestion in that, although the small intestine's lactase activity was lower in late preterm infants, late preterm infants could adapt to lactose feedings. It is hypothesized that this adaptation is made possible by resident intestinal microbrials. These microbials can ferment lactose into 2 and 3 carbon chains and in turn make energy via the lactose salvage pathway. Despite these adaptations, late preterm infants may experience a range of feeding requirements ranging from lactation support in both inpatient and outpatient settings to total parenteral nutrition for infants with respiratory failure who are administered inhaled nitric oxide. Despite the aforementioned adaptations, a number of factors have been identified in previous studies as important developmental intestinal immaturities believed to be related to feeding problems.

Coordination of the suck-swallow reflex for example, does not generally take place until 34 weeks' gestation. Also, intestinal microflora play an important role in determining overall nutrition, development of the intestine, as well as maturation of both innate and adaptive immunity. Imbalance in this intestinal microbial environment may detrimentally influence health in the short term via necrotizing enterocolitis and in the long term in the form of allergies, asthma and auto-immune disorders such as Type-1 diabetes. Therefore gastric motility which is less developed, may in turn predispose the late preterm infant to a greater risk of bacterial overgrowth versus infants born at term.[92] Consequently late preterm infants may experience greater rates of feeding difficulties in addition to a variety of morbidities in the short and long term. [167] Feeding difficulties in turn are associated with longer hospital stays.

The degree of colonization by intestinal microbials evolves with time, ranging from zero organisms or sterility at birth to heavy colonization characterized by greater than 10^{13} microorganisms made up of 500 species in adulthood. Resident microflora play key roles in nutrition, angiogenesis and mucosal functioning, thus in large part both infants and microorganisms benefit from symbiotic interactions which take place in the intestine. Removal of resident bacteria demonstrates the beneficial role resident bacteria play, as reduction or removal via infection by other organisms or antibiotic administration may block uptake of important nutrients or impair normal immune function.[147] More specifically for the late preterm infant admitted to the NICU, treatment with antibiotics, complete parenteral feeding or incubation may interfere with colonization of the intestine, and may increase susceptibility to infection.

Breast feeding

Breast feeding late preterm infants may be complicated compared to term infants for a number of reasons.[172] As a consequence of developmental immaturity, late preterm infants may be sleepier and have less stamina. An underdeveloped nervous system may lead to poor coordination of the suck-swallow reflex and infants may have trouble latching onto the mother.[119] Similarly, late preterm infants may have delayed bilirubin excretion. Achieving optimal lactation support through breast feeding may also be hindered by multiples, diabetes, pregnancy induced hypertension, prolonged rupture of membranes, chorioamnionitis, oxytocin, induction, or a cesarean section.[175] When both infant and/or maternal factors limit breast feeding, late preterm infants may be at a greater risk of hypothermia, hypoglycemia, excessive weight loss, slow weight gain, failure to thrive, prolonged artificial milk supplementation, exaggerated jaundice, kernicterus, dehydration, fever resulting from dehydration, and rehospitilization.[86]

Few studies have quantified feeding problems in late preterm infants. In Seubert's[149] study of 553 infants born between 32 and 36 weeks' gestation at a tertiary care hospital, there was a significantly greater incidence of feeding problems for infants born before 34 weeks ($p<0.04$). Wang et al[168] reported that 27% of late preterm

infants versus 5% of term infants required intravenous infusions, which was thought to be a consequence of hypoglycemia resulting from poor feeding. In the same study, feeding problems were a frequent cause of prolonged hospitalization. According to Adamkin[1], these results are not surprising considering late preterm infants typically need considerable aid in attaining consistent nutritive breast feeding. As mentioned, to improve nutritive feeding, late preterm infants may be administered total parenteral nutrition and/or enriched formulas. A study by Adamkin et al[1] reported that infants with Bronchopulmonary Dysplasia, a chronic lung disorder that results from prolonged ventilation for infants with respiratory distress, total parenteral nutrition may provide nutrients not provided by poor breast feeding. Accordingly, complications of failed breast feeding including dehydration and hypoglycemia may be prevented.

1.6.4.2 Necrotizing Enterocolitis

Necrotizing entercolitis is a condition in which various regions of the bowel undergo necrosis or tissue death. NEC may be observed in late preterm infants, however it is most common (80 to 90%) in very low birth weight infants. The incidence of necrotizing enterocolitis in late preterm infants is unknown, however risk factors significantly associated with NEC include low Apgar scores, chorioamnionitis, exchange transfusions, prolonged rupture of membranes, congenital heart disease and neural tube defects.[31,36]

1.6.5 Hypoglycemia

1.6.5.1 Outcomes

A number of previous studies have demonstrated a higher incidence of hypoglycemia among late preterm infants relative to term infants. Wang's study reported hypoglycemia more often in infants born at 35 to 36 weeks gestation (15.6% vs 5.3%; OR; 3.30, 95% CI; 1.1-12.2; P = 0.028, FE) than in term infants. Previous studies

have demonstrated that glucose is the primary substrate of cerebral metabolism. Although other substrates are available for the brain of the developing late preterm infant, even mild or moderate hypoglycemia has the potential to impair neurodevelopmental processes, which may in turn influence long term neurodevelopment outcome. Insufficient ketogenic responses in late preterm infants further enhance the potential for neurological injury. A variety of neurological insults are associated with sustained or recurrent hypoglycemia. One study demonstrated that when hypoglycemia was observed on 5 or more separate days, the incidence of developmental delay increased 3.5 times. Prolonged hypoglycemia was associated with seizures, permanent neuronal injury and death in one study.

Glucose is a vital requirement for the developing fetus, accounting for approximately 80% of the energy consumed by a fetus. Glucose is supplied by the mother, transplacentally via facilitated diffusion. In order to ensure a concentration gradient for facilitated diffusion, fetal glucose levels are kept at concentrations that are approximately 2/3 to 4/5 of maternal glucose levels. Following birth and the clamping or cutting of the umbilical cord, an infant must quickly and efficiently adapt his or her metabolism to produce glucose independently. The transition to endogenous glucose production is characterized by an initial drop in glucose concentration from 2/3 to 1/3 relative to the mother in the first 2 to 4 hours following birth. A number of studies indicate that glucose levels in late preterm infants may drop lower, (2.652 to 3.536 mmol/L) than typical term levels (3.536 to 5.304 mmol/L). [12] Concentrations of enzymes responsible for hepatic glycogenolysis and hepatic ketogenesis rise, attenuating the risk and incidence of hypoglycemia. As a consequence of developmentally immature hepatic glycogenolysis, adipose tissue lypolysis, hormonal dysregulation, deficient gluconeogenesis and ketogenesis, late preterm infants may be at a greater risk of hypoglycemia. Until metabolic pathways can compensate or exogenous sources of glucose are supplied, glucose concentrations will likely fall. Energy demands further enhance the risk of hypoglycemia if the infant is exposed to infection,birth asphyxia and/or cold stress[64]. Within 12 to 24 hours, a well adapted newborn can stabilize glucose levels within the 3.33 to 4.44 mmol/L range. [58] An

estimated eight percent of infants however, fail to successfully transition during this period and require therapeutic intervention to treat hypoglycemia [58]. According to Garg and Devaskar[58],the process of labor may provide hormones and enzymes necessary for ensuring benign glucose concentrations. In term infants these mechanisms maintain euglycemia and protect against adverse long term neurodevelopmental outcome. Glucose metabolism in late preterm infants has not been well studied, consequently current understanding is poor.

A previous study has observed delayed hepatic glucose-6-phosphatase activity in late preterm versus term infants. G-6-P activity is important because this enzyme catalyzes the final step in both hepatic gluconeogenesis and glycogenolysis. In addition to lower G-6-P activity, decreased gastrointestinal immaturity may lead to less enteral intake which combined with a poorly coordinated suck-swallow reflex may limit glucose intake. Together delayed hepatic glucose-6-phosphatase action, limited enteral intake and an uncoordinated suck-swallow reflex may together and individually provide potential explanations for the higher incidence of hypoglycemia in late preterm infants[114]. More specifically, the available literature does indicate an inverse relation between gestational age and the incidence of hypoglycemia. Furthermore, Wang et al [168]observed that late preterm infants require glucose infusions on average more than term infants, indicating to Wang that late preterm infants may be at a greater risk of hypoglycemia.

According to Garg and Devaskar, transient and persistent hypoglycemia in late preterm infants may also be associated with a number of maternal conditions and neonatal conditions. Maternal conditions associated with transient hypoglycemia in late preterm infants include glucose infusion in the mother, preeclampsia, diabetes, drugs including tocolytics and sympathomimetics. Neonatal conditions associated with transient hypoglycemia include prematurity, respiratory distress syndrome, twin gestation, neonatal sepsis, perinatal hypoxia-ischemia, temperature instabililty/hypothermia, polycythemia, glucose transporter deficiency, isoimmune thrombocytopenia, or Rh incompatability.

1.6.7 Liver

1.6.7.1 Outcomes

Watchko et al[171] state that hyperbilirubinemia requires evaluation and treatment more often than any other condition in the newborn infant. A retrospective study of 51 387 infants conducted by Newman et al[125] indicates that late preterm infants may be 7.4 (5.2%) times more likely to develop hyperbilirubinemia than term infants (at 41 weeks 0.7%). Interestingly, even infants born between 36 and 37 weeks were 5.7 times more likely to experience significant hyperbilirubinemia versus term infants born at 39 to 40 gestational weeks. In the same study, the incidence of hyperbilirubinemia dropped linearly at approximately 0.6 times per completed week of gestation. In another retrospective study of infants requiring phototherapy and readmission, infants were grouped by gestational age. Infants born between 35 to 36 weeks' (245–252 days'), 36 to 37 weeks' (253–259 days'), and 37 to 38 weeks' (260–266 days') gestation had 13.2, 7.7, and 7.2 fold greater risk of hyperbilirubinemia respectively than infants born $\geq$ 40 weeks' gestation. In a prospective study conducted by Sarici et al[138], infants born between 35 to 37 weeks developed hyperbilirubinemia 2.4 times more often than infants born between 38 to 42 gestational weeks. In a study of clinical outcomes of infants born between 35 to 36 6/7 weeks' gestation, more late preterm infants were clinically jaundiced than term infants born between 37 to 40 weeks' gestation (54.4% vs 37.9%; OR: 1.95; 95% CI: 1.04–3.67; P = .027, FE). From the same study, the same clinically jaundiced infants, as well those infants exhibiting poor feeding had longer hospital stays. In a longitudinal study comparing infants born between 35 to 37 weeks' gestation(245 to 265 days) to infants born between 38 to 42 weeks' gestation(266-294 days), the incidence of significant hyperbilirubinemia requiring phototherapy was more than two fold greater in the 35 to 37 weeks' gestation group (n=37, 25.3%) as compared to the term group (n=23, 10.5%). There were also significant differences in Apgar scores, hematocrit and mode of delivery between late preterm and term infants. The

incidence of extreme hyperbilirubinemia in a study examining all infants born at 37 weeks' gestation or greater in Denmark between Jan 1 2000 to Dec 31 2001(n=128 433) and late preterm (35 to 36 weeks), was 25 per 100 000.[45] A number of etiologies were thought to be responsible for the cases of extreme hyperbilirubinemia observed including severe haemolytic disease (n=2, 6%), ABO blood type incompatibility (n=13, 41%), haematoma (n=2, 6%), hypothyreosis / hypothyroidism (n=1, 3%), diabetic mother (n=1, 3%), and maternal hypogalactia/abnormally low milk secretion (n=3, 9%).

1.6.7.2 Developmental Immaturity and Hyperbilirubinemia

Late preterm birth is one of the most commonly identified risk factors for the development of severe hyperbilirubinemia.[154,156] In the majority of infants, hyperbilirubinemia represents a temporary, harmless transition to extrauterine life. If left untreated, hyperbilirubinemia can lead to harmful total serum bilirubin levels resulting in bilirubin encephalopathy or kernicterus with both morbidities potentially causing brain damage.[17] According to Watchko, the late preterm infant is incapable of dealing with conjugated bilirubin due to a number of developmental immaturities. Late preterm infants, like term infants, become jaundiced as a consequence of a greater concentration of bilirubin entering the hepatocytes. A study by Kawade and Ohishi[97] has demonstrated less activity of the uridine diphosphate glucuronyl transferase enzyme. This results from decreased erythrocyte survival, greater erythrocyte volume, greater enterohepatic circulation of bilirubin, decreased uptake of bilirubin from blood plasma and defective bilirubin conjugation. These deficiencies are believed to help explain the higher rates of hyperbilirubinemia, with greater severity and duration among late preterm infants. A number of risk factors for hyperbilirubinemia which carry the potential for subsequent kernicterus have been identified in late preterm infants including; breast milk feeding, large for gestational age, male gender, glucose-6-phosphate dehydrogenase deficiency and breast-feeding. The evidence for each will be assessed in turn.

Breast milk feeding as a risk factor for hyperbilirubinemia in the late preterm infant was assessed in two studies. In Bhutani et al's US Pilot Kernicterus Study[18], breast milk feeding was the risk factor most commonly associated with hyperbilirubinemia. Poor suck swallow coordination may lead to breastfeeding difficulties resulting potentially in dehydration. Dehydration may increase the risk of hyperbilirubinemia by increasing the enterohepatic circulation of bilirubin which in turn can increase the amount of bilirubin reaching the liver. Because the immature newborn's gastrointestinal tract has yet to be colonized by symbiotic bacteria which convert conjugated bilirubin to urobilinogen, both enterohepatic circulation of bilirubin and intestinal β-glucuronidase activity are high. One breast feeding study observed that jaundice may be associated with caloric deprivation resulting in greater enterohepatic circulation of bilirubin. Any further increase in bilirubin levels above already high levels, from poor breast feeding for example, may place the late preterm at a greater risk of significant hyperbilirubinemia.

Large for gestational age status as mentioned, was also identified as a risk factor. Along with large for gestational age, other risk factors for hyperbilirubinemia included oxytocin induction, vacuum or forceps delivery and cutaneous bruising. The US Pilot Kernicterus study also found that almost 2 times as many males (n=84) as females (n=38) entered the study with kernicterus. A rat model of kernicterus supports these variations in sex, as male rats have been observed to exhibit greater permeability of the blood brain barrier to unbound bilirubin, greater passage of bilirubin through neuronal plasma membranes and higher total serum bilirubin levels. [25] As well as sex differences in central nervous system binding, metabolizing and clearing of bilirubin have been observed. Results from the US Pilot Kernicterus registry also indicate that individuals who were deficient in glucose-6-phosphatase, an X-linked disorder, made up 20.8% of the population. Individuals born late preterm, G-6-P deficient and breast fed, comprised 60% of the prevalent cases of hyperbilirubinemia with an odds ratio of 10.2 (1.35 to 76.93) comparing infants with these three risk factors to those without these three risk factors.

1.6.8 Immune System and Infection

Previous studies have established that both the central nervous system and the respiratory system undergo a great deal of maturation during the third trimester, continuing up to the last few gestational weeks. Presently, it is uncertain whether the immune system undergoes maturation of similar magnitude during the final weeks of the third trimester. Although the degree to which developmental immaturity predisposes the late preterm infant to an increased risk of infection remains unclear [33], previous studies do indicate that the underdeveloped immune system of the late preterm infant may contribute to a greater incidence of sepsis.[20] For example, a higher incidence of microbial infections has been reported among term newborns as compared to children and adults. [33] Extremely preterm infants with the most underdeveloped immune system tend to be most susceptible to infection as evidenced by studies reporting incidence rates of infection among extremely premature newborns(<28 weeks gestation) that are 5 to 10 times higher than term and children or adults [32]

Thus, when comparing newborns of any gestational age to children and adults, developmental immaturity appears to predispose newborn infants to a greater risk of infection. [33] However, the developmental sequence of the immune system in the late preterm infant has not been studied and is not well understood. Nevertheless, a study by Wang et al, reported the odds of evaluation for sepsis which included imaging studies, complete blood cell counts, blood cultures and intravenous antibiotics, was 3.97 (95% CI: 1.82–9.21) comparing infants born at 35 to 36 6/7 weeks' gestation to infants born between 37 to 40 weeks' gestation. The higher rate of evaluation for sepsis however, may be a consequence of confounding by indication and should be interpreted with caution.

The timing, associated morbidities as well as the pathogenic organisms responsible for infection in late preterm infants have been studied in some detail. In a retrospective study of 207 infants born between 34 and 36 weeks' gestation the proportion of infants with sepsis remained relatively constant between 34(5.0%) and

35(5.6%) weeks, however no infants developed sepsis at 36 weeks. [7] In assessing the literature, very few studies, have specifically examined the immune system of the late preterm infant, nor quantified the incidence of infection in this population. Accordingly, the developmental regulation and incidence of infection in the late preterm infant requires further research. [33]

Infections in late preterm infants are grouped into three broad temporal categories; prior to delivery, termed congenital infection, during delivery and presenting within 72 hours of life, termed early onset, and in the hospital presenting after 72 hours of life, termed late onset. [15]According to Benjamin[15], neonatal infections among late preterm infants are a major problem because infections may lead to neonatal complications, longer hospital stays and higher mortality rates. Importantly, the clinical presentation of congenital and perinatal infection may be similar despite the variety of potential infectious agents. Cytomegalovirus, rubella, toxoplasmosis and syphilis typically present with intrauterine growth resitriction, jaundice, rash, intracranial calcifications, microcephaly, chorioretinitis and thrombocytopenia(low platelet count). Sequelae which result from congenitally acquired infections are generally observed at birth, however some sequelae may not present until months or years down the road, and may include auditory impairment, visual impairment potentially leading to blindness, as well as developmental delay.

Congenital infections are most commonly caused by *Toxoplasma gondii*, rubella virus, cytomegalovirus, herpes virus, HIV, parovirus B19 and *Treponema pallidum.* A number of studies indicated that the risk of transmission from mother to fetus increases with increasing gestational age. For example, studies examining *Toxoplasma* transmission rates indicate that rates are lowest in the first trimester (less than 5%) and highest(approximately 60%) in the third trimester. Also, an association between gestational age and severity of infection has been reported. More specifically, congenital toxoplasmosis and rubella infections, occurring in the first trimester, are associated with greater rates of stillbirth and congenital anomalies[15].

Early onset infections pose a threat to the health of the late preterm infant generally through a different group of organisms. In addition to exposure and colonization of the gastrointestinal tract by a number of generally benign microbials (*Lactobacillus, Peptostreptococcus, Saccharomyces*), the late preterm infant may also be exposed to pathogenic organisms including group B streptococcus, *Escherichia coli* and *Candida*[28]. A number of risk factors are associated with higher incidence of early onset sepsis in neonates including preterm delivery, rupture of membranes lasting greater than 18 hours, maternal fever and chorioamnionitis.[14] Early onset sepsis may be associated with temperature instability, lethargy, irritability, apnea, respiratory distress, hypotension, bradycardia, tachycardia, cyanosis, abdominal distension, hyperglycemia, jaundice, and feeding intolerance.

Late onset sepsis may be a consequence of perinatal or postnatal microbial infection, but more commonly late onset sepsis results from nosocomial transmission. Microbial organisms generally responsible for late onset sepsis include *Staphylococcus aureus*, *Candida* species and gram-negative rods.[51] *S. aureus* remains a problem mainly because of the emergence of methicillin-resistant strains, while *Enterococcus faecalis* and *Enterococcus faecium* remain an important pathogen as these organisms are potentially resistant to vancomycin.[52] A variety of risk factors are associated with late onset sepsis including younger postconception age, longer NICU stays, central vascular access, invasive procedures and broad-spectrum antibiotics (for example third generation cephalosporins).

1.6.9 Respiratory System

1.6.9.1 Outcomes

Respiratory Distress Sydrome

Late preterm birth is associated with a higher incidence of respiratory distress, transient tachypnea of the newborn[86], persistant pulmonary hypertension of the newborn and hypoxic respiratory failure. [34] In a study by Wang et al, late preterm

infants were diagnosed with respiratory distress 6.88 times more often than full-term infants (28.9% vs 4.2%; OR: 9.14; 95% CI: 2.9–37.8; $P < .00001$, FE).Similar trends were observed in an American retrospective study using the Kaiser Permanente cohort in Oakland California. The frequency of respiratory distress was 22.1% for infants born between 33 to 34 weeks of gestation, 8.3% for infants born at 35 to 36 weeks, and 2.9% for infants born between 37 to 42 weeks. [49] Respiratory distress rate trends held in two Italian studies as well. In the first Italian prospective cohort study, the rate of respiratory distress was 20.6% among babies born at 33 to 34 weeks, 7.3% among babies born at 35 to 36 weeks', and 0.6% among babies born at 37 to 42 weeks. [144] In a second Italian study examining all infants(n=63 537) born in 65 hospitals in 17 regions of Italy, 734 (1.16%) were diagnosed with respiratory distress syndrome, of which the fatality rate was 24% (n=176). In the same study the Italian authors used Wald's test and the Chi-squared statistic to test for risk factors. Gestational age, type of delivery, birthweight, sex and maternal age were found to be associated with respiratory distress syndrome. Multivariable regression and odds ratio with 95% Confidence Intervals supported gestational age, birthweight, maternal age as risk factors, as well mode of delivery and male gender.

In another study of respiratory problems in late preterm infants, three groups were established, 34 weeks gestation (n=370), 35 weeks gestation (n=783) and 36 weeks gestation (n=1696). In this cohort, 7.3% of infants developed respiratory distress syndrome. There was no statistically significant difference in the proportion of infants born at 34 or 35 weeks who developed RDS (p=0.116), however a statistically significant difference was observed when comparing the proportion of infants developing RDS in 34 and 35 week infants to infants born at 36 weeks (p<0.001). [92]

1.6.9.2 NICU and Health Services

According to Laptook and Jackson[106], the severity of respiratory distress often determines the level of care after birth. Therefore, in addition to incidence rates of respiratory morbidities, a limited number of studies have assessed the need for

various respiratory interventions[41] as well as rates of NICU admission. For example, Escobar et al studied short term outcomes among late preterm infants. Of the 1011 infants who were intubated and ventilated, more than half (55%) required surfactant. From the same cohort, infants born between 33,34,35 and 36 weeks' gestation, the adjusted odds ratios for ventilation were 28.8 (CI 20.4 to 40.6), 18.67 (14.0-24.9), 8.76(6.77 to 11.4) and 4.95 (3.95 to 6.21) comparing each respective gestational week to infants born at term. The odds ratios indicate an increased need for supplemental oxygen with decreasing gestational age. A similar inverse relation held for assisted ventilation.[49] In a study of infants born between 35 to 36 weeks, 8% required supplemental oxygen, a rate that was approximately three fold greater than the reference population of infants born at 37 weeks gestation or later. [49] In a Brazilian study assessing resuscitative procedures in late preterm infants at birth, of the 1054 late preterm infants studied, 338 (32%) received only free-flow oxygen, 143 (14%) were bag and mask ventilated, and 27 (3%) were intubated. [3]

In Clark's prospectively collected cohort study of 1011 infants who were born at greater than 34 weeks' gestation and intubated within 72 hours of birth(and expected to be ventilated for more than 6 hours), 437 or 43% were diagnosed with respiratory distress syndrome, meconium aspiration syndrome in 98 (9.7%), pneumonia/sepsis in 84 (8.3%), and transient tachypnea of the newborn in 40(4.0%). More than half of infants were administered surfactant (n=558 or 58%). In assessing relevant morbidity rates, chronic lung disease was diagnosed in 11% of ventilated infants (n=109) and the mortality rate was 5% (n=51) among this group of ventilated infants. Progressive respiratory distress was believed to be the cause of death in 11 or 21% of cases. Clark assessed risk factors for death using multivariable regression and found that a major anomaly (adjusted OR=23, CI=11 to 54, $p<0.001$); an Apgar score less than 5 at 5 minutes (adjusted OR=6.4, CI=2.5 to 16, $p<0.001$); treatment with extracorporeal membrane oxygenation (adjusted OR=5.9, CI=2 to 18, $p=0.001$); and treatment with inhaled nitric oxide (adjusted OR=2.5, CI=1.0 to 5.6, $p=0.04$) were associated with a greater risk of death. Administration of surfactant was associated with a lower risk of adverse neurological event (adjusted OR=0.5, CI=0.3 to 0.8, $p=0.005$).

In another study of health services use in late preterm infants, three groups were established; 34 weeks gestation (n=370), 35 weeks gestation (n=783) and 36 weeks gestation (n=1696), and 4.6% needed assisted ventilation. The proportion of infants born between 34 and 36 6/7 weeks who were admitted to the NICU was 24.9%. The length of stay in hospital for infants admitted to the NICU compared to infants not admitted to the NICU remained relatively constant with each increasing week of gestation. More specifically, for infants born at 34, 35 and 36 weeks, the infants admitted to the NICU stayed 3, 4 and 3.5 times longer than infants not admitted to the NICU. A decrease in the odds of NICU admission was observed with increasing gestational age. The odds dropped from 47.4 between 34 and 35 weeks to 41.9 between 35 and 36 weeks. The odds of RDS dropped by 25.4%, while the odds of assisted ventilation dropped by 39.1%.[92] In a retrospective study of 207 infants born between 34 and 36 weeks' gestation, the proportion of infants admitted to the NICU decreased significantly with each additional week from approximately half to 14.8% and 7.5% for 34, 35, and 36 weeks respectively($p<0.001$). Infants born at 34 weeks had birthweights that were significantly lower compared to infants born at 35 and 36 weeks. The proportion of infants developing respiratory distress decreased with each additional week from 15%, to 13% to 3.2% for infants born at 34, 35 and 36 weeks' gestation. [7]

1.6.9.3 Development of the Respiratory System

Important progress is made in the developing fetal lung between 34 to 37 weeks' gestation. Specifically, the lining of alveolar saccules, the terminal respiratory units of the lung, develops from cuboidal type II and flat type I epithethial cells to alveloli. These more developmentally mature alveoli have a lining which is composed in large part of thin type I epithethial cells. As alveoli mature, pulmonary capillaries simultaneously grow into each terminal sac and the fetus produces surfactant volumes that are similar to adult levels. Failure to complete the processes comprising this developmental stage, termed the alveolar period, is associated with delayed intrapulmonary fluid absorption, surfactant insufficiency and inefficient gas

exchange. [90] In addition to the developmental changes that occur within the fetal lung, biochemical and hormonal changes accompany spontaneous birth and vaginal delivery. These changes are believed to play an important role in facilitating the newborn's transition to extrauterine life. [44] It is through these biochemical changes, that lung fluid clearance is thought to take place, which allows ventilation and gas exchange to occur across the newborn's lungs [85,87]. An important result of these biochemical changes should include greater blood flow directed to the lungs, which in turn ensures ventilation can be balanced with perfusion. [11] Failure to undergo spontaneous labor, clear lung fluid or mirror ventilation with perfusion may place the late preterm infant at a greater risk of respiratory distress syndrome. [44]

Presently, the precise mechanism by which the fetus and/or the newborn achieve clearance remains uncertain. Recent studies indicate that lung clearance, via transepithethial movement of alvelolar fluid, may be due in larger part to amiloride-sensitive epithethial sodium channels. Greater production of mRNA coding for amiloride-sensitive epithelial channels has been correlated with proper lung clearance, while disruption of these channels has been correlated with higher rates of respiratory distress syndrome and transient tachypnea of the newborn.[11] Although cardiovascular physiology has not been examined to a great extent in the late preterm infant, cardiovascular function is thought to be impaired as a result of both structural and functional underdevelopment, which in turn limits cardiovascular reserves in times of stress. Respiratory distress in the late preterm is believed to be complicated by immature cardiovascular function resulting from delayed closure of the ductus arteriosus and may also be complicated by persistent pulmonary hypertension.[144]

1.6.9.4 Respiratory Distress and Cesarean Section

Birth by cesarean section, as compared to spontaneous vaginal delivery has been observed to be associated with a higher incidence of respiratory morbidity. A meta-analysis by Hansen et al[72] examining the relationship between cesarean section and

respiratory morbidity assessed nine studies. These studies compared vaginal delivery to cesarean section and found a greater risk(although not always statistically significant) of a variety of respiratory morbidities across all studies. In general, although variation in study design existed, the risk of respiratory morbidity increased approximately two to three fold with cesarean section, with the magnitude of risk believed to be dependent on gestational length [72]. In addition to higher rates of respiratory distress syndrome associated with elective cesarean section, late preterm infants have also been observed to experience higher rates of transient tachypnea as well as persistant pulmonary hypertension.[56,76]

1.6.9.5 Transient Tachypnea

In a study by Clark, transient tachypnea was diagnosed in 594 (0.93%) infants, and 8(1.3%) died from TT. Risk factors associated with TT were gestational age, type of delivery, maternal diseases, twin pregnancy, birthweight and gender. These risk factors were supported by multivariable regression models and odds ratio with accompanying Confidence Intervals.

1.6.9.6 Hypoxic Respiratory Failure in the Late Preterm Infant

The incidence of hypoxic respiratory failure in late preterm infants is unknown, however it is believed to be low. According to Dudell and Jain[44], hypoxic respiratory failure is believed to be an important cause for high rates of NICU admission among late preterm infants. Further studies focused on hypoxic respiratory failure in late preterm infants is necessary. [44]

1.6.9.7 Apnea

It has been hypothesized that late preterm infants are at a greater risk of developing apnea because of a developmentally immature central nervous system that is deficient in myelin, and has fewer sulci and gyri than the full-term brain.[27,39] The observation that the late preterm brain is 65% of the weight of the term brain and has five fold less

volume, is believed to contribute at least in part to the differences in incidence among late preterm and term infants. The incidence of apnea in late preterm infants has been observed in some studies to be about four fold higher in late preterm infants as compared to term infants ranging from 4% to 7% in near term infants as compared to 1% to 2% in term infants. Risk factors associated with apnea in late preterm infants in these studies include a higher susceptibility to hypoxic respiratory depression, reduced chemosensitivity to carbon dioxide, immature pulmonary irritant receptors, increased respiratory inhibition, sensitivity to laryngeal stimulation, and reduced upper airway dilator muscle tone. A greater risk of apnea in infants has not been observed across all studies. For example, in Wang et al's study, there was no statistically significant difference in the frequency of apnea or bradycardia in near-term vs full-term infants (4.4% vs 0%; $P = .054$).

1.7 Limitations of Available Literature

The late preterm literature currently consists of many reviews, and few original studies assessing outcomes. Wang et al's study is almost universally cited in the late preterm literature and in many cases provides the only or defining evidence for the idea that morbidity is higher among late preterm infants. This study although a well conducted study in a number of respects, compared 95 term infants to 90 late preterm infants not born between 34 to 36 weeks' gestation, but rather between 35 to 36 6/7 weeks. Accordingly, Wang's results should be compared and interpreted cautiously with the aforementioned limitations in mind. The available population based studies suffer from a number of limitations. The use of death certificates in large population based studies provides limited information on causes of death. No information was available from autopsy findings, which would be useful in clarifying causes of sudden infant death syndrome. Furthermore information on exact gestational age is important in comparing outcomes stratified by gestational age, however any variation may be non-differential and thus may impact both groups similarly. Two recent, potentially important population based studies comparing mortality in term and late preterm

infants included congenital anomalies. Prospective data collection is required to confirm the overall excess in mortality observed by Young et al[180]and Tomashek et al's[163]comparison of mortality in late preterm and term infants.

Antenatal Risk Factors

Previous studies have found a greater risk for indicated or spontaneous birth among mothers with medical conditions including hypertensive disorders of pregnancy, diabetes and asthma. Only one previous study[118] has examined the relationship between maternal medical conditions and newborn morbidity among late preterm infants during the birth hospitalization. This population based study compared late preterm infants to term infants born between 37 to 41 weeks gestation. This assessed the individual and joint effects of eight antenatal conditions including hypertensive disorders of pregnancy, diabetes, antepartum hemorrhage, lung disease, infection, cardiac disease, renal disease and genital herpes. With the exception of genital herpes, each maternal condition was associated with a greater risk of morbidity in both term and late preterm infants as compared to mothers without the condition. Importantly, the independent effect of late preterm birth was approximately seven fold greater than the independent effect of any maternal condition and adjustment for potential confounders did not alter the results substantially. Of note, certain maternal conditions such as antepartum hemorrhaging and hypertensive disorders of pregnancy were observed to interact, leading to a multiplicative increase in morbidity rates rather than a simply additive effect.

1.8 Research Gap

This study will attempt to fill, at least in part, one of the gaps identified by a Clinical Report prepared by the National Institute on Child Health and Human Development's Committee on the Fetus and Newborn, for 2006 and 2007. This report outlined the need for; "identification tools, educational programs, and screening strategies to identify risk factors and prevent potential medical complications of late-preterm births". Accordingly this manuscript will attempt to develop a prognostic model that

could be used as an identification or screening tool for respiratory disorders. This study will be original in that no studies have been conducted with the specific aim of assessing late preterm morbidity in Southwestern Ontario, and no studies have been conducted on a Canadian population with the specific aim of predicting the risk of morbidity among late preterm infants. A recently published article in Pediatrics which assessed the effect of Late Preterm Birth and Maternal Medical Conditions on Newborn Morbidity Risk[118] called for the evaluation of maternal morbidity on specific newborn conditions including respiratory distress syndrome, persistent pulmonary hypertension, sepsis, and jaundice among late preterm infants. The authors stressed that further research into these areas was an important and critical issue and should be the subject of future research. The author of the present manuscript identified this gap well before this call for further research was published. This manuscript will be important in filling this now publicized gap by providing a prognostic model aimed at predicting respiratory problems in term and late preterm infants.

Neonatal respiratory disorders including transient tachypnea of the newborn and respiratory distress syndrome can have devastating consequences. More specifically, complications of respiratory distress syndrome may include intraventricular hemorrhage, bleeding in the lung, bronchopulmonary dysplasia, delayed cerebral development, mental retardation, retinopathy of prematurity and blindness. Furthermore, RDS is the most common cause of death in the neonatal period. Thus, serious morbidity and mortality is possible with respiratory problems and a tool with the ability to differentiate high from low risk infants is necessary in not only limiting mortality and morbidity, but also in limiting health care spending that may result from rising numbers of late preterm infants. This tool may also guide timing of deliveries by decreasing deliveries among infants at high risk of respiratory problems while potentially improving the timing of delivery of infants at low-risk of respiratory problems. Subsequently, improving timing could decrease mortality and morbidity. Predicting respiratory problems however, is complicated by the fact that although many late preterm infants appear healthy at birth, late preterm infants have been dubbed the "great imposters"[53] due to the fact they are developmentally immature as compared to term infants and are at a much higher risk of

mortality and morbidity. Therefore an ability to capture inherent patterns in the St Joseph's Health Care administrative database so that a prognostic model can be generated and applied to future patients (at St Joseph's and other hospitals), would be highly valuable. Previous studies have identified risk factors for respiratory problems; however this study will for the first time combine maternal characteristics with infant characteristics at birth in order to predict the risk of respiratory problems.

Chapter 2: Research Objectives

The specific objectives are as follows:

1. To develop a prognostic model capable of predicting respiratory disorders among infants born at $\geq$ 34 weeks gestation and $\leq$ 41 weeks gestation

2. To determine the frequency of neonatal morbidity and intervention use among Late Preterm Infants admitted to the perinatal level III unit (NICU) in London, Ontario, Canada

3. To compare neonatal morbidity rates between Late Preterm (34 to 36 weeks gestation) and Term Infants (37 to 41 weeks gestation)

Chapter 3: Methods

3.1 Design

A hospital-based retrospective cohort, drawing on all singleton birth records at St. Joseph's Health Care, London Ontario, was used to conduct the present study.

3.2 Sample Size

The existing obstetrical and NICU databases at St. Joseph's Health Care contained information on 34,714 infants. The available data determined the sample size, thus sample size calculations were not performed.

3.3 Data Sources

The administrative obstetrical database at St Joseph's Health Care contains information on each mother's obstetrical history. Guided by the Vital Statistics Act, the database was constructed using prospectively collected data on all deliveries of infants greater than or equal to 500g and greater than 20 weeks gestational age. Accordingly, non-participation is not a limiting factor in this study. To construct the database, data collection for mothers included abstraction of all relevant information from the medical record. In addition to the obstetrical database, St Joseph's Health Care maintains an NICU database which records various neonatal clinical outcomes among infants admitted to the NICU. Maternal characteristics were connected with NICU outcomes by linking the obstetrical and NICU databases, using the mother's identification number and date of birth. All identifiers were then removed. The NICU database only contains data on infants admitted to the NICU, and follow up information extends from birth until discharge from the NICU.

3.5 The Study Population

3.5.1 Inclusion Criteria

The study included all singleton deliveries at St. Joseph's Health Care in London Ontario between January 1, 1996 and December 31, 2006. Mothers were from Southwestern Ontario and surrounding areas. St. Joseph's Health Care, London, Ontario, is a tertiary perinatal centre and consequently, high risk expectant mothers

from outside of Middlesex County may be transferred to St. Joseph's. Mothers were predominantly from Middlesex County, however there were mothers from Windsor, Toronto, Kitchener/Waterloo and as far north as Thunder Bay. In an effort to improve clinical relevance and applicability, these births were included.

3.5.2 Exclusion Criteria

Twin and multiple gestations were excluded from analyses because the incidence of multiple births is associated with higher rates of prematurity and perinatal mortality[5]. Infants with a congenital anomaly were excluded as anomalies are also associated with prematurity and mortality. This study focuses on clinical outcomes among infants born at 34 weeks gestation or later. Accordingly, infants born before 34 weeks and after 41 weeks gestation were excluded. Infants with birthweights less than the 3rd percentile were deemed small for gestational age, and infants >97th percentile were deemed large for gestational age. Both small and large for gestational age infants have different risks of morbidity and mortality than infants of normal birth weight (3rd to 97th percentile) and were excluded from all analyses.

3.6 Generalizability and Validity

The reference population to which generalizations may be extended, includes all singleton births in Canada at tertiary care centers. As mentioned, the study population includes singleton deliveries from mothers in Southwestern Ontario and surrounding areas between January 1, 1996 and December 31, 2006. The generalizability of study results may be limited by a lack of data from two other Middlesex County hospitals.

In addition to deliveries at St. Joseph's Health Care, infants may also be delivered at Strathroy Middlesex General Hospital and London Health Sciences Centre, Victoria Hospital in London, Ontario. Strathroy Middlesex General Hospital is a small hospital serving a rural catchment area surrounding Strathroy and no data were analyzed from this site. Likewise, neither obstetrical nor NICU data were available from Victoria hospital. Thus, Middlesex County infants delivered at either of these hospitals will not be captured by this study. As mentioned some high risk deliveries

will be transferred to St. Joseph's Health Care and will be included in the analyses. The generalizability of the results may be influenced by the potential for more high risk deliveries to occur at St. Joseph's Health Care where Level III NICU facilities are available. Women may also choose between the three hospitals based on geography, religion or personal preference, however these factors are not believed to affect relations with covariates and outcome. Thus, due to the fact that every birth occurring at St Joseph's should be captured, it is likely that internal validity will be strong and the results will be important for neonatologists managing the 4500 births that occur each year at St Joseph's Health Care in London. Furthermore, the results of this study are likely generalizable to any Level III Perinatal Centre in Canada, however generalizing further will require context specific judgement.

3.7 Defining Late Preterm Birth

For analysis purposes, the reference group included infants born at term (37 to 41 weeks gestation). Gestational age estimates were based on the best obstetrical estimate using the mother's last menstrual period and any ultrasonography during pregnancy. Last menstrual period was used if first trimester ultrasound was within four days of the estimated date of delivery or second trimester ultrasound was within 10 days of the estimated date of delivery. Gestational age was otherwise based on ultrasonographic measurements routinely obtained during early pregnancy for dating purposes. Gestational age was not rounded up. More specifically if an infant was born at 34 weeks and 4/7days, the infant was coded as 34 weeks. Gestational age was conceptually categorized into two groups including infants born at 34 to 36 and $\geq$37 weeks gestation. These categories are consistent with the National Institute of Child Health and Human Development's definition of late preterm and term birth. Before categorizing the gestational age for analysis purposes, gestational age was examined as a continuous variable to determine if it was normally distributed. The minimum, maximum, mean and median gestational ages were determined for comparisons against Canadian and American distributions. The results are provided in Figure 1 (in the results section).

3.8 Outcome Pertaining to Objective 2 and 3

Comparisons of morbidity rates and intervention requirements were made between late preterm infants and term infants. Dichotomous morbidities assessed included; respiratory distress syndrome, transient tachypnea, apnea/bradycardia, neonatal sepsis (including infections of the blood, urinary tract and cerebral spinal fluid), patent ductus arteriosus, intracranial hemorrhage, necrotizing enterocolitis, periventricular leukomalacia and retinopathy of prematurity. Interventions assessed included: mechanical ventilation, surgery, and surfactant administration. Continuous outcomes compared included days on continuous positive airway pressure (CPAP), days of supplemental oxygen, days of mechanical ventilation, days to full feeds and length of stay in the NICU.

The following helps define how morbidities were diagnosed. Apnea and bradycardia were defined as a clinically significant apneic or bradycardic episode (apneic episode >15 seconds, nonsleeping heart rate <80 bpm) on a record entry specific for cardiorespiratory events. Respiratory distress syndrome was defined as a need for oxygen supplementation for greater than 24 hours with typical diagnostic imaging findings. Transient tachypnea of the newborn was defined as oxygen supplementation for less than 24 hours with typical diagnostic imaging findings, including increased vascularity and interstitial lung fluid. Periventricular leukomalacia was defined as evidence of cerebral white matter damage occurring in a characteristic distribution consisting of periventricular focal necroses with subsequent cystic formation and more diffuse white matter injury. Necrotizing enterocolitis, a syndrome resulting from intestinal necrosis, was diagnosed as $\geq$ stage 2 by the Bell Classification.[13] Patent ductus arteriosus was diagnosed clinically and or with a 2-D echocardiogram. Retinopathy of prematurity was diagnosed according to the International Classification Consensus Conference definition.

3.9 Statistical Analyses Pertaining to Objectives 2 and 3

Dichotomous morbidities and interventions were compared using Pearson chi-square tests and Risk Ratios with their respective 95% confidence intervals. Continuous outcomes including length of stay were compared using two-sample t-tests and ANOVA. To compare medians among ordinal variables including APGAR scores and length of stay, the Wilcoxon rank sum test were used. Statistical analyses were performed using SAS version 9.1 (SAS Institute, Carey, NC) and the R statistical package (2.6.2) with Harrell's Design and Hmisc libraries. The probability of developing respiratory disorders and the c-index were obtained by using the "lrm" and "nomogram" functions of the Design library. Unless otherwise noted, a p value of ≤ 0.05 was deemed statistically significant.

3.10 Outcomes Pertaining to Objective 1

Maternal and neonatal characteristics were used to predict respiratory disorders. In this study, respiratory disorders were defined as an infant diagnosed with one of the two most common acute respiratory disorders, namely respiratory distress syndrome or transient tachypnea of the newborn. Considering the time frame of the information collected on infants in the database, an infant could only develop one of the above morbidities between birth and discharge. The following will detail the factors considered in constructing a predictive model for respiratory disorders.

3.11 Prognostic Modeling

Obtaining an accurate estimate of an infant's prognosis is important for multidisciplinary health care teams and families alike. Thus, the overarching objective was to capture inherent patterns in the administrative database so that a prognostic model could be generated and applied to future patients at St Joseph's Health Care and other level III tertiary care centers. The prediction model developed in this study will be used to predict respiratory disorders including respiratory distress syndrome and transient tachypnea of the newborn, among term and late preterm

infants. The formula for the prediction model can be represented mathematically as follows:

$$\log\left(\frac{\text{risk of respiratory disorders}}{\text{1-risk of respiratory disorders}}\right) = \text{linear predictor}$$

$$= \beta o + \beta_1 \text{ x predictor1} + \ldots + \beta_n \text{ x predictor}_n$$

where Bo is the intercept and β_1 to β_n represent regression coefficients from the binary logistic regression model. The results for the univariable and multi-variable logistic regression models are provided in Table 13 and in the Appendix.

Guidelines set out by Harrell [73] were applied to potential predictors, missing data, overfitting and violated assumptions.

3.12 Predictor Variable Selection and Omitted Predictors

Preliminary deletion of variables that are either measured poorly or not likely to be predictive of outcome can lead to models with less overfitting and more generalizability [70].The first step in developing the predictive model was to clearly define the relationship of interest. The predictive ability of maternal obstetrical and neonatal characteristics with respect to late preterm morbidity was of particular interest in this study. More specifically, respiratory disorders were the focus. Accordingly, a composite outcome consisting of both respiratory distress syndrome or transient tachypnea of the newborn served as the response variable and was termed respiratory disorders. One-hundred and fifty three variables from the obstetrical database were available as potential predictors.

3.12.1 Candidate Variables from the Literature

Few studies have assessed risk factors for respiratory distress syndrome(RDS) and transient tachypnea(TT) in newborns. In 1981, Hjalmarson[77] found that respiratory distress was associated with gestational age, birthweight, sex and postnatal asphyxia, while in 1996 Bonafe and Rubalteli[22] found RDS was associated only with gestational

age and birthweight. Most recently in 1999, Dani et al[38], found that gestational age, birthweight, maternal age, male gender and cesarean section were associated with respiratory distress. Dani et al[38] also studied transient tachypnea and found that TT was associated with gestational age, maternal diseases, twinning, birthweight, operative vaginal delivery, cesearean section and male gender. For the purposes of this study, twinning was not assessed, nor was the broadly defined predictor 'maternal diseases'. Birth asphyxia was not available in the database, but a proxy for birth asphyxia based on an arterial pH of <7.01, Apgar <5 at 5 minutes and base deficit > 15 was possible. Only 0.25% met the criteria and therefore it was decided that each component predictor of birth asphyxia would be examined individually.

3.12.2 Other Predictor Variables

Linking the obstetrical and NICU databases led to a combined total of 153 variables. A subset of variables was selected based on a review of the literature and on clinical relevance as determined by an experienced neonatologist. The literature review was conducted by the author and verified by an experienced librarian. The variable selection process was done in conjunction with an experienced neonatologist and thus any missing or omitted predictors are likely due to publication bias, absence of the variable from the database or limiting variable decisions to two individuals' experience and knowledge of the literature. Table 1 outlines the definition and coding of the predictor variables used.

Some categorical variables were recoded to minimize categories for analysis. Category amalgamation was based on the criteria of clinical relevance and the ease of obtaining predictor variables in routine clinical practice. Furthermore, previous validation studies have reported inaccuracies associated with administrative databases that attempt to differentiate chronic from pregnancy induced conditions. Accordingly, a number of categorical variables were grouped or dichotomized. Diabetes was dichotomized into absent (0 or 1 from Table 1) and present (2 to 4 from Table 1) because it is difficult to differentiate chronic diabetes from pregnancy induced diabetes using administrative data and it was not deemed important to differentiate

these conditions for the purposes of this study. Premature rupture of membranes (PROM) was re-coded to present or absent. To assess the potential effects of rupture of membranes more than 24 hours prior to onset, further analyses were conducted for rupture <24 hours prior to onset of labour and rupture ≥24 hours prior to onset of labor. Labour was dichotomized as present or absent. Meconium was dichotomized to absent and present (thin or thick). Delivery type was dichotomized to vaginal birth or cesarean section as the level of detail present in the database was not deemed useful for the purposes of this study. Furthermore this level of detail may not be readily available, which would limit generalizability

Hypertensive disorders of pregnancy was a variable created for this study from three existing variables: chronic hypertension, pregnancy induced hypertension and hypertension complications (Table 1). Smoking included any smoking during pregnancy. Maternal chronic hypertension (when analyzed separately from hypertensive disorders of pregnancy), clinical chorioamnionitis, oligohydramnios, polyhydramnios, intrapartum fever, meconium, were all dichotomous predictors coded as present or absent. Gestational weeks (34 to 41 weeks gestation), APGAR scores at 1 and 5 minutes (range 1 to 10), arterial pH (7.34 to 7.45)[29], arterial base excess, mother's age were continuous and were modeled as continuous variables.

3.13 Modeling of Continuous Variables

Categorizing continuous variables may represent a somewhat subjective process that leads to variables with less statistical information. Furthermore, categorization does not reduce measurement error, but instead may lead to the placement of subjects in the incorrect category leading to 100% error. Thus, throughout the multivariable modeling process, categorization of continuous variables was avoided. In some exploratory analyses the literature was used to guide categorical cut points. Overall, however restricted cubic splines was the method of choice for relaxing linearity assumptions where indicated. According to studies conducted by Stone[159], the placement of knots when using restricted cubic splines is generally not crucial. Rather

Stone has found that model fit depends more on the number of knots, with 3 knots generally needed for samples less than 100 and up to 5 knots needed for samples greater than 100. Since knots may use up degrees of freedom, knots can be used conservatively based on the relative importance of a predictor.[73] Accordingly, gestational weeks was modeled using five knots, while birth weight, arterial pH and arterial base excess were modeled with three knots.

3.14 Exploratory Univariable Analyses

Graphical and univariate analyses were conducted to assess the appropriateness of linear associations with outcome on the logit scale. The literature was used to guide categorization of continuous variables. Maternal age was categorized into <20, 20-34 and >35 years of age using dummy variables which replace the linearity assumption with an assumption of homogeneity within each category. The young and old maternal age groups were compared to the middle age group. Similarly, birth weight was divided into quintiles and compared to the middle group, while gestational age was divided into 34,35,36 weeks and compared to all infants born at 37 weeks or later. Furthermore it was the intent of the authors to compare late preterm infants to infants born at term, thus 37 weeks or greater was assumed homogeneous for the unique purposes of this study.

As mentioned, failing to consider missing data, potential predictors, overfitting and violated assumptions may lead to model inaccuracies. [73]

3.15 Missing Data

Hospital protocol at St Joseph's requires recording all maternal and neonatal characteristics in the medical record and storing them in the obstetrical and NICU databases. As well, all data are collected in a short time frame, between admission and discharge and thus very little loss to follow up is expected. The data management team at St Joseph's Health Care London has maintained the database for over 20 years and is experienced in collecting, inputting and maintaining the quality of the data. The extent to which missing data influences the results is expected to be

minimal, but represents a limitation of the study nevertheless. Considering both the data collection protocols, the quality control measures and the expected extent of missing data, a complete case analysis was planned. Assuming data are missing completely at random relies upon two assumptions. The first being that the rate of missing data is not related to outcome. The second assumption rests on assuming that variables such as Apgar scores are missing regardless of high or low values. [54] Since, Apgar scores are automatically collected, data are likely to be missing equally for high and low values and it will be assumed that missingness is unrelated to high or lower values. Accordingly, subjects with missing data will be discarded and a complete case analysis will be conducted. Various authors provide rules of thumb for missing data ranging from 5 to 20%. To be conservative, a complete case analysis was planned if there is missing data for $\leq 5\%$ for one variable.

3.16 Overly Influential Observations

Overly influential observations are an important consideration because the method employed to validate the model, bootstrapping, relies on sampling with replacement. Accordingly, influential or extreme values of predictor variables could seriously affect the fitting and validating processes. Univariable frequencies were obtained and all maximum and minimum values were assessed. Where clear data transcription errors existed, these case entries were deleted. Deletion of any extreme values could inflate the predictive model's accuracy. Accordingly, no extreme values were deleted, guarding against potential model accuracy inflation.[73]

3.17 Correlation and Collinearity

To assess correlation among predictors, a Spearman Correlation Matrix was constructed. Generally when considering causal modeling, the stability of regression coefficients may be compromised by the inclusion of two highly correlated variables. However, it has been recognized that this is not a concern in predictive modeling in that although correlation may indicate collinearity, collinearity does not influence predictions based on the same data set or on new data. This assumption holds if the new data have the same degree of collinearity. Only gestational age and birth weight

were correlated (r=0.65). It was assumed that gestational age and birthweight would maintain the same degree of collinearity in new data and thus both birthweight and gestational weeks were included in the model.

3.18 Distributional Assumption

By definition, the logistic model is a direct probability model. This follows from the fact that it is described in terms of Prob(Y=1)x). Because the distribution of a binary random variable Y can be defined by the probability that Y=1 and since no distributional assumptions are made about the predictors, the logistic model does not make any distributional assumptions about predictors and outcomes.[73]

3.19 Linearity Assumption

Built into a binary logistic regression model is the assumption that the predictor variable is linearly related to the log odds of the response (log(P/(1-P)) where P is the probability of the response). The assumption of linearity on the logit scale was assessed for each of the predictors by visually inspecting the levels of each predictor plotted against the sample risks.

3.20 Additivity Assumption

A lack of interaction or an assumption of additivity for the effects of the predictors is also an assumption that is made when constructing logistic regression models. In assessing the literature, Kinney et al[92] found that an infant's brain at 34 weeks gestation is only 2/3 of the volume of a term infant. Similarly, late preterm infants have less developed respiratory, gastrointestinal and immune systems than term infants[34]. Furthermore, higher rates of morbidity and mortality have been observed among this group, including respiratory disorders.[45] Thus, gestational weeks is believed to be a biologically plausible effect measure modifier. In considering gender as a possible effect measure modifier, male infants have been observed to develop respiratory disorders more frequently than female infants, potentially arising from developmental differences due to gender. Accordingly, it is hypothesized that

gestational weeks and gender may modify the association between maternal characteristics and respiratory disorders. However, due to a lack of available reporting of interactions in the literature it was not hypothesized nor certain that other interactions exist. The Chunk Test, a global test for interactions was performed testing all interactions and ignoring all higher order interactions. In total, 166 interactions between 28 variables were assessed. It was hypothesized a priori, that due to both the large sample size and the biologically plausible potential for interaction, the Chunk Test was likely to be statistically significant.

3.21 Confounding

Confounding is typically assessed after considering possible interactions because estimates of association may otherwise be incorrect. Of note, in analytic and explanatory modeling, a clear differentiation is drawn between exposures and confounders. Conversely, predictive modeling does not distinguish between these two types of variables, but rather each independent or predictor variable takes on the same role [35],ie as a potential risk factor. Accordingly, confounding will not be considered specifically in the predictive model building process.

3.22 Data Reduction and Overfitting Considerations

The desire to limit the number of predictors to those that are likely to be predictive of outcome and reliably estimated was motivated by a desire to avoid overfitting. This is because a model with less variables that are predictive and reliably estimated may contribute to greater generalizability.[73] A rough guideline was used to assess if 28 variables represented too many variables. Harrell et al[70] suggest that to generate a model with predictive discrimination that is valid on a new sample, there must be at least n cases of the outcome, (respiratory disorders),/10 to fit a multiple regression model. From the database, 523 cases of respiratory disorders were available. Thus, the model could be fit with up to 52 degrees of freedom. Since 22 degrees of freedom were used for 22 main effects, 5 for interactions with sex and 12 for interactions with gestational age, 39 degrees of freedom would be used in total, well under the upper

limit of 58. Accordingly, it was assumed that there was likely to be no problems associated with overfitting, and thus data shrinking methods were not applied.

3.23 Statistical Analyses Pertaining to Objective 3

It has been argued that it is advisable to limit the use of stepwise variable selection because stepwise variable selection does not deal with overfitting and may reduce the available information. Furthermore, a number of authors concur that leaving all clinically relevant variables in the model, rather than discarding variables based on p-values, generally leads to models with better discrimination.[59] With these concerns in mind, full and simplified models were constructed. Simplified models with fewer variables were constructed using backwards stepwise regression with a stay level of significance of p=0.50 and using the Akaike Information Criteria as a stopping rule. Although overfitting is not a concern with 22 variables, it is important to limit the number of available variables to a number that is clinically useful and readily available. A correction or penalization factor was applied for using backwards stepwise regression when using the validate and calibrate functions in R.

3.24 Models Constructed

Data were analyzed using unconditional multiple logistic regression models with maximum-likelihood estimation of parameter values to obtain odds ratios.

Model 1

Using binary logistic regression, Model 1 was generated to serve as a comparison against which variable grouping, modification and transformations could be judged. Aside from diabetes and labour, all variables were left ungrouped or continuous and no transformation or relaxing of linearity assumptions was employed.

Model 2

Respiratory disorders were modeled using binary logistic regression with all predictor variables. Model 2 made use of two composite variables; hypertensive disorders of pregnancy and bleeding.

Model 3

Respiratory disorders were modeled using binary logistic regression and the literature was used to guide the construction of dummy variables aimed at relaxing linearity assumptions on the logit scale for all continuous variables. Each gestational week was compared to 39 weeks gestation.

Model 4

Respiratory disorders were modeled using binary logistic regression with all of the same factors as model 4, however gestational age was categorized to 34,35,36 and ≥37 weeks gestation.

Model 5

Model 5 built upon model 4 by including all statistically significant and biologically plausible interactions.

Model 6

Model 6 employed restricted cubic splines in order to relax linearity assumptions for continuous predictors.

Model 7

Model 7 built upon model 6 by including statistically significant and biologically plausible interactions. This will be referred to as the full model.

Model 8

To this point all models have incorporated all predictor variables with the aim of progressively improving prediction. In an effort to simplify the model for use in a clinical setting, model 8 attempted to reduce the number of variables by reverse stepwise logistic regression using a conservative stay level of significance of 0.50.

Model 9

Model 9 applied backwards elimination using Akaike' Information Criterion as the stopping rule.

Model 10

Model 10 assessed the predictive ability of the top 8 variables from Table 16, which ranks the individual c-indexes and Somers' D values.

3.24.1 Quantifying Predictive Accuracy

Measuring predictive accuracy is important in quantitatively appraising each model's predictive ability. Predictive accuracy can be subdivided into calibration and discrimination. As part of bootstrapping, discrimination measures a predictor's ability to differentiate different patients with different outcomes while calibration assesses the extent to which bias has influenced the accuracy of the predictive model.

3.24.2 Discrimination

The c-index, or concordance index is a measure of predictive discrimination. It is identical to the area under a receiver operator curve and estimates the probability of concordance between predicted and observed responses.[71] Liu and Dyer[111] advocate the application of rank association measures such as the c index in quantifying the impact of risk factors in epidemiologic studies. The c-index provides an estimate of the probability of concordance between predicted and observed responses. C-indexes are somewhat limited however in that the method of ranking assumes the (prediction, outcome) pairs (0.01,0), (0.9,1) as no more concordant than the pairs (0.05,0),(0.8,1.0). Accordingly the c-index cannot precisely differentiate small changes in discrimination ability between two models. A c-index of 0.5 provides no predictive discrimination, while a value of 1.0 indicates perfect sensitivity and specificity, ie a perfect ability to differentiate people with and without disease. A value of 0.8 shows good discrimination[68]. Some may find a symmetric scale more intuitive. For a rank correlation coefficient ranging from -1 to +1 with 0 indicating no

correlation, Somers' D rank correlation can be calculated as follows; 2(c-0.5). Both measures will be used in this study to quantify predictive ability.

3.24.3 Calibration

As mentioned, calibration refers to the extent of bias, or more specifically to the agreement between predicted risks and observed frequencies of respiratory disorders. Calibration was assessed using both the slope and intercepts obtained using the validate function in Harrell's Design library and by a calibration plot using the calibrate function which provides both an estimate of error and visual representation of the differences of the apparent and bias corrected slope compared to the ideal slope. Perfect calibration is indicated by a calibration slope of 1 and a calibration intercept of 0. A calibration intercept >0 indicates that the model's predicted probabilities are systematically too low, while a calibration slope of <0 indicates predictions are systematically too high. A calibration slope below 1 indicates that the regression coefficients were too high leading to low predictions being too low and high predictions being too high. A calibration slope above 1 indicates that the regression coefficients were about zero.

3.24.5 Model Validation

Ideally a model's predictive ability is tested via an external validation study on a different population, however such a population was not available. According to Harrell[73], many models fail external validation tests because overfitting is not rigourously or honestly assessed. To obtain nearly unbiased internal tests of accuracy, a variety of methods for internal validation were considered including data-splitting, cross validation and boot-strapping. Data splitting will not be employed because splitting the data reduces the sample size and power. Furthermore, simulation studies have demonstrated high variability between different splits of the data. Cross validation was not used because previous studies indicate the accuracy of predictions generated by cross validation have a high degree of variability when the cross validation procedure is repeated. Accordingly, bootstrapping will be used for internal

validation purposes. The validate function was used to perform a resampling validation of the logistic regression model in order to obtain a bias-corrected Somers' Dxy rank correlation, the calibration intercept and the calibration slope of an overall logistic calibration. The calibration function in R was used to generate the calibration curve for the predictive model.

3.24.6 Internal Validation Using the Bootstrap

Assessing internal validity is important in determining the predictive ability of the model on future patients at St Joseph's Health Care London. The process of internal validation requires fitting and validating the model on the same series of patients used to develop the model and bootstrapping was the method of choice. Efron[55] found in simulation studies that bootstrapping provides nearly unbiased estimates of predictive accuracy with comparatively low variance. Furthermore, bootstrapping is performed on the entire sample, providing a clear advantage over data splitting and cross validation which both split the sample into model building and validation samples.

3.24.7 A Brief Overview of the Process of Bootstrapping

Step one involves fitting the full model with an elimination or stepwise procedure for example and obtaining a Somer's D, called $D_{apparent}$. A bootstrapped sample is generated with replacement and a model is fit with the same elimination or stopping rule as for $D_{apparent}$, and a Somer's D is obtained called $D_{bootstrap}$. The reduced model obtained from fitting the model on the bootstrapped sample is then tested on the original sample, a Somer's D is obtained and termed $D_{original}$. Optimism or O, in the fit is calculated by $O=D_{bootstrap}-D_{original}$ and the aforementioned steps are repeated 100s to 1000s to obtain 100's or 1000's of O's, which are averaged. To obtain the bootstrap corrected performance of the original stepwise logistic regression model, $D_{apparent} - O$ can be obtained. The difference is equal to a nearly unbiased or honest estimate of the expected value of Somer's D and is a measure of internal validity.

3.25 The Nomogram

The nomogram is a graphical representation of the multivariable binary logistic regression model. The nomogram provides the estimated probability of an infant developing respiratory disorders given a specific level of a continuous variable or presence or absence of a dichotomous variable. The relative contribution of each predictor is indicated by the width of the predictor axis. Gestational weeks spans the width of the nomogram indicating that it provides greater predictive ability relative to other factors such as presence of labour. To obtain the probability of respiratory disorders from Figures 6 and 7, draw a straight line from each predictor axis up to the Points axis for each predictor. Total the points obtained from all predictors, and connect a line from the total points axis down to the probability axis to obtain the estimated probability of respiratory problems.

Table 1. A listing of the candidate predictor variables used in both univariable and multivariable logistic regression modeling.

Dichotomous Predictors	**Original Coding in the Database** **(Coding for the Purposes of this Study)**
Preeclampsia/Eclampsia (PIH)	0=None; 1=Gestational hypertension; 2=Mild pre-eclampsia; 3=Severe pre-eclampsia; 4=Eclampsia (Present(1 to 4) or Absent(0))
Chronic Hypertension	Present or Absent (Present or Absent)
Hypertension Complications	0=None; 1=End-organ involvement (1 or more of proteinuria,elevated liver enzymes, and/or low platelet count); 2=HELLP (hemolysis and elevated liver enzymes and low platelet count). (HELLP Present or HELLP Absent)
Hypertensive Disorders of Pregnancy (HDP)	A composite of Chronic Hypertension, PIH and HELLP
Clinical Chorioamnionitis	Present or Absent
Oligohydramnios	Present or Absent
Polyhydramnios	Present or Absent
Maternal Intrapartum Fever	Present or Absent
Alcohol Use	Yes or No
Drug Use	Yes or No
Gender	Male or Female
Placenta previa	Present or Absent
Placental abruption	Present or Absent
Other Bleeding	Present or Absent
Bleeding	A composite of Placenta previa, Placental abruption and other bleeding
Maternal Diabetes	Diabetes was coded in the database as 0=No; 1=Carbohydrate intolerance (1 abnormal reading on a 75 gram oral glucose tolerance test (GTT);2=Gestational onset, diet controlled; 3=Gestational onset, insulin controlled; 4=Overt. (Present (2 to 4) or Absent (0 to 1))

Premature rupture of membranes (PROM)	The membranes must have ruptured 1 or more hours prior to the onset of labour. PROM was coded in the database as 0=No;1=Ruptured 1-5 hours PRIOR to the onset of labour; 2=Ruptured 6-24 hours PRIOR to the onset of labour; 3=Ruptured > 24 hours PRIOR to the onset of labour (Ruptured < 24 hours vs > 24 hours)
Delivery Mode	1=Vertex; 3=Breech; 4=Assisted breech; 5=Extracted breech; 6=Other or unknown type of vaginal birth; 7=C/S low segment; 8=C/S T-incision; 9=C/S vertical; 10=Other C/S (Vaginal delivery (1 to 6) or Cesarean Section (7 to 10))
Labour	1=Spontaneous onset of labour with no use of oxytocin AND no ARM prior to onset of active labour (ie regular uterine activity, a cervix that has reached 3-4 cm and is thinning); 2=Induction (cervical ripening with Foley, Prostaglandins, Misoprostil and /or administration of oxytocin/ARM prior to onset of active labour (regular uterine activity, cervix 3-4 cm and thinning)); 3=C/S no labour i.e., COLD C/S (Labour Present (1 or 2) or Labour Absent (3))
Smoking	Yes or No
Meconium	Meconium was coded in the database as absent, thin or thick (Present (thin or thick) or Absent)
Continuous Predictors	
Gestational Weeks	Completed weeks gestation
Apgar score at 1 minute	Score from 1 to 10
Apgar score at 5 minutes	Score from 1 to 10
Arterial pH	1 to 14
Arterial base excess	
Mother's Age	Measured in Years
Infant birthweight	Measured in grams

Chapter 4: Results

4.1 Characteristics of all singleton births at St. Joseph's Hospital between January 1 1996 and December 31 2006.

Gestational ages of births reported in the database ranged from 25 to 44 weeks with a high density of births around term gestation (Figure 1). The range of gestational ages spanned from 25 to 44 weeks gestation. The mean gestational age for the population studied was 38.7 weeks (S.D. 2.34). The median was 39.0 weeks and the mode was 40.0 weeks. Among the 34714 infants analyzed, 31235 infants were born at 37 weeks gestation or later, while 3479 infants were born preterm or before 37 weeks gestation. The overall rate of preterm birth was 11.14%.

Analyzing birth weight as a continuous variable indicated an approximately normal distribution with a slight negative (left) skew (Figure 2). The mean birth weight among term infants was 3502.78g (SD =485.46, Min 777 and Max 6915 g) as compared to a mean of 2238.85g (SD=771.01, Min = 355g and Max =4490g) for preterm infants (Table 2). For comparison purposes, mean birth weights ranged from 2123 g for infants born at 34 weeks gestation to 3745 g for infants born at 41 weeks gestation according to a Canadian birth weight study conducted by Kramer[98].

4.2 The Study Sample: Late Preterm Birth

Figure 3 displays how the study sample was obtained based on exclusions, missing data and errors/implausible values. As outlined in the methods section, anomalies(n=89), births before 34 weeks(n=1406), birth after 41weeks gestation (n=117) and infants that were small or large for gestational age(n=1996) were excluded from analyses. There was missing data for the following continuous variables; arterial pH(n=1679), base excess(n=1719), gender data(n=10), maternal age (n=5), PROM (n=5), labour type(n=3) and diabetes(n=1).
Of the 34714 infants studied, 325, 517 and 957 were born at 34, 35 and 36 weeks gestation respectively. Thus a total of 1799 infants were born late preterm and the late

preterm birth rate was 6.09%. The mean birth weights for infants born at 34, 35 and 36 weeks gestation were 2399.24g (SD= 473.24, SE=24.06, Min=1085, Max=4415), 2585.73g (SD=469.73,SE=19.39, Min=770, Max=4156) and 2867.12g (SD=458.26,SE=13.85, Min=1285, Max=4490).

Gender frequencies stratified by gestational age (Table 3), indicate that more males are born late preterm and at term than females with gender proportions approaching equivalency with increasing gestational age. For gestational ages ≥37 weeks, the proportions are nearly evenly split, however the genders do differ by 1.96% over the 37 to 41 week span.

4.3 Mode of Delivery and Labour

Table 4 provides the frequency of delivery variables. The frequency of spontaneous labour decreased with increasing gestational age in this study. As gestational weeks increased, the proportion of spontaneous and induced labours approached equivalency with cesarean sections accounting for fewer deliveries with increasing gestational age. For infants born at ≥37 weeks, almost all infants were born to mothers who underwent either spontaneous or induced labour. There was no clear trend among late preterm infants with respect to cesearean section rates. For readers attempting to assess the generalizability of study findings, frequencies for maternal and newborn characteristics are provided in Tables 5 and 6.

4.4 Errors or Implausible Values

As mentioned in the methods, since the bootstrapping procedure samples with replacement, extreme or overly influential observations could compromise the bootstrapping procedure. Accordingly, values were deleted if they were entered in obvious error or were biologically implausible. Apgar scores at 1 minute(n=250) and 5 minutes (n=227) less than zero and arterial pH values greater than 14(n=12) were deleted.

4.5 Correlation and collinearity

Only gestational age and birthweight were found to be correlated (r=0.65) and both were included in multivariable analyses.

4.6 Linearity Assumptions

The assumption of linearity on the logit scale was assessed for each of the predictors by visually inspecting the levels of each predictor plotted against the sample risks. Arterial pH, arterial base excess, gestational age, maternal age and birth weight indicated evidence of non-linearity on the logit scale. Accordingly, each of these predictors was modeled using restricted cubic splines.

4.7 Results of Assessment of Additivity Assumptions

A small number of the interactions(n=4) among variables other than gender and gestational weeks reached statistical significance. However, these interactions were neither biologically plausible, nor defined a priori and were assumed to represent spurious statistical significance. A number of interactions between gender or gestational age with various maternal variables reached statistical significance. To test interactions individually with gender and gestational age, all other maternal variables were combined with gender or gestational age. Of the 28 interactions tested with gestational age, 10 were statistically significant (α=0.05), while 3 predictors indicated a statistically significant interaction with gender. All 12 statistically significant interactions were considered for inclusion in the full model.

4.8 Mortality

The overall perinatal mortality rate defined as stillbirth and neonatal death through 28 days of age for all age groups in the study sample was 2.29 deaths per 1000 births. Overall there were 76 deaths among the 33 220 term and late preterm infants in the study (Table 7). These figures as indicated by the table include still births and congenital anomalies. After excluding anomalies, survival rates among term and late preterm infants are close to 100% across all gestational ages in the study.

4.9 Morbidity

The proportion of infants admitted to the NICU dropped with increasing gestational age and similar trends were apparent when comparing morbidity rates and intervention use among late preterm infants to term infants (Tables 8,9,10,11). With the exception of intracranial hemorrhage which is an uncommon outcome in late preterm and term infants[153], morbidity rates and intervention use are universally higher among late preterm infants at 34, 35 and 36 weeks gestation compared to term. Infections recorded in Table 12 include endotracheal tube infections (n=11), cerebral spinal fluid infections (n=2) and blood infections (n=40). In considering all term and late preterm infants included in the study, only 53 infants developed infections according to the database. Among late preterm infants, 25 of 2066 (1.2%) and 28 of 31154(0.09%) term infants developed sepsis. The highest Risk Ratio for morbidity in comparing late preterm to term infants was respiratory distress syndrome, an important finding in the context of this study. Infants born at 34 weeks are at a much higher risk than any other gestation, and important differences in risk are evident even when comparing infants born at 36 weeks to infants born at term.

4.10 Results of Univariable Logistic Regression Analyses

4.10.1 The Predictors

Initially all predictor variables were individually regressed on the outcome, respiratory disorders. In one set of analyses, most predictors were analyzed without grouping. Thus chronic hypertension and pregnancy induced hypertension were analyzed separately while birth weight, maternal age and gestational age were analyzed as continuous variables. With the exception of chronic hypertension, maternal age, bleeding, meconium, smoking, drug use and alcohol use during pregnancy, all predictors were statistically significant at α=0.05. The results of these analyses are presented in Table 13.

In considering validation studies which report that administrative databases may fail to accurately differentiate chronic conditions like hypertension from the pregnancy induced form; chronic hypertension was grouped with pregnancy induced hypertension(PIH), and HELLP (hemolysis, elevated liver enzymes and low platelet

count) to form a new variable called hypertensive disorders of pregnancy. Chronic hypertension alone failed to reach statistical significance, but PIH reached statistical significance. The composite variable, hypertensive disorders of pregnancy, failed to reach statistical significance.

Similarly, differentiating gestational from pregnancy-induced diabetes was not deemed to be important or advisable based on the administrative nature of the data. The p-value for diabetes was 0.41 and the odds ratios included one, providing no statistically significant evidence that diabetes is linearly related to the log odds of respiratory disorders.

In assessing the results of maternal bleeding analyses, both previa and abruption were significantly associated with respiratory disorders in univariable logistic regression analysis. The variable, "Other Bleeding" failed to reach statistical significance. It was not deemed clinically important to differentiate the various forms of bleeding including placental abruption, placenta previa and "Other Bleeding". Placental abruption, placenta previa and Other Bleeding were thus grouped as Bleeding During Pregnancy.

The presence of labour has been observed to trigger hormone regulated maturation of the fetal lung leading to lung clearance and surfactant production[42]. Accordingly, the presence of labour was hypothesized to be very important in predicting respiratory disorders. When comparing both spontaneous and induced labour to cesearean section, the odds of respiratory disorders was similar and both were statistically significant. It was assumed for the purposes of this study that spontaneous and induced labour could be grouped together, as both achieve the same result; labour.

Maternal age was initially analyzed as a continuous variable resulting in rejection of the null hypothesis that maternal age is linearly associated with the log odds of respiratory disorders. In assessing the literature, studies examining maternal age often group mothers into <20, 20 to 34 and >35 years of age. Accordingly, maternal age

was categorized using dummy variables with the middle age group, 20-34 used as the reference. Comparisons of infants from mothers who were <20 years of age to mothers 20-34 years of age failed to reach statistical significance. Similarly, comparisons of mothers older than 35 years of age to mothers 20 to 34 years of age also failed to reach statistical significance. Accordingly, these results provide no evidence of a difference in respiratory disorders when comparing young and old mothers to the middle aged group of mothers.

Birth weight modeled as a continuous predictor linearly related to the log odds of respiratory disorders reached statistical significance. However, respiratory disorders have been reported with high and low birth weights. Accordingly, birth weight was split into quintiles representing the 10^{th},(<2865g), 10^{th} to 25^{th} (2865 to 3150g), 25^{th} to 75^{th} (3150 to 3775g), 75^{th} to 90^{th} (3775 to 4045g) and >90^{th}(>4045). The third group, (3150 to 3775 g) was used as a reference. Only one of the four birth weight categories that was compared against the reference was statistically significant, indicating a significant difference in predictive ability comparing infants in the <10% percentile category to the reference (25^{th} to 75^{th} percentiles for birthweights included in this study). In addition to being statistically different, the odds ratio is also empirically much higher for this group than all other groups compared to the 25^{th} to 75^{th} percentile.

4.10.2 The Outcome: Respiratory Disorders

Respiratory disorders have been reported for early and late gestational ages. To assess the degree to which these previous findings hold in the present sample, a frequency table was constructed for respiratory disorders by gestational week (Table 14). From this table, it appears that 39 weeks represented a nadir. Accordingly, each gestational week from 34 to 44 was compared to 39 weeks. A clear drop in odds ratios towards the null is evident from 34 to 40 weeks gestation. The risk levels out considerably at term or 37 weeks, is relatively stable between 40 and 41, weeks but rises again at 42 weeks to a level nearly equivalent to 37 weeks. Although the frequency of respiratory disorders drops to 0 for 43 and 44 weeks, this result is based on only four infants and

previous studies have demonstrated a higher risk of respiratory disorders in this age group.

4.11 Results of Multivariable Logistic Regression

Figure 4 provides a quick and easy method of assessing the directional effect of each predictor using Model 1, as well as the degree of error involved in the estimated effect measure. Odds ratios of less than one indicate a protective effect while odds ratios greater than 1 indicate a greater risk of respiratory disorders. An odds ratio that is on both sides of one represents an odds ratio that has failed to reach statistical significance. Wide confidence intervals indicate imprecisely estimated odds ratios, while more narrow intervals indicate more precisely estimated effect measures. Figure 4 indicates that later gestational ages, higher Apgar scores, female gender and higher arterial base excess levels are protective, while chorioamnionitis, intrapartum fever, absence of labour, cesearean section, and higher birthweight increase the risk of respiratory disorders after adjusting for all other predictor variables. Hypertension, PIH, PROM, Diabetes, bleeding, arterial pH, maternal age, smoking, drugs and alcohol exposure during pregnancy, oligohydramnios, polyhydramnios and meconium did not reach statistical significance at $\alpha=0.05$.

Model Considerations

Taking into consideration the potential inaccuracies of administrative databases, and the desire to be clinically useful, only models incorporating the aforementioned grouping and dichotomizing of labour, bleeding, diabetes, and hypertensive disorders of pregnancy were considered as potential multivariable models. The first step in generating the multivariable model was to compare c-indexes for all predictor variables in order to assess both the individual and combined improvements in prediction that were possible. This was also helpful in seeing the relative magnitude of the predictive ability for each predictor, which may be helpful in assessing the implications of each variable's presence or absence. Table 15 provides a ranking of the c indexes and allows one to assess how much each predictor may individually improve prediction above chance. The two variables with the highest predictive

discrimination are gestational age and APGAR score at 1 minute. Individually, the c-indexes are 0.759 and 0.729 respectively, however together the c-index is 0.838. Combining gestational weeks and birth weight only increases the c-index to 0.766 and combining APGAR score at 1 minute with birth weight yields a c index of 0.767. Accordingly, gestational age in combination with other predictor variables is likely crucial in predicting respiratory disorders.

4.12.1 Model 1

The results of the modeling process are included in the appendix.

Pr (Respiratory disorders) = Gestational Weeks + Birth weight + Apgar 1 + Apgar 5 + Delivery Mode + Labour + Hypertension + Pregnancy Induced Hypertension + Chorioamnionitis + Oligohydramnios + Polyhydramnios + Smoking + Drugs + Alcohol + Diabetes + Previa + Abruption + Other Bleeding + Arterial pH + Arterial Base Excess + Fever + Meconium + Gender + Maternal Age

This model has good discrimination at c=0.85, but failing to relax linearity assumptions may lead to model inaccuracies. For the logistic regression model fit, gestational weeks, other bleeding, diabetes, smoking during pregnancy, chorioamnionitis, intrapartum fever, APGAR scores at 1 and 5 minutes, arterial base excess and gender reached statistical significance at $\alpha=0.05$, providing evidence that the regression coefficients were different than 0 and the odds ratios were different than 1 after adjusting for all other variables in the model. Of note, both placenta previa and placental abruption failed to achieve statistical significance, while the variable other bleeding achieved statistical significance. In assessing the marginal significance of other bleeding ($\alpha=0.04$), the apparently low predictive ability (c=0.504), the potential inaccuracies associated with administrative data and the need for simplicity, other bleeding was grouped with placenta previa and placental abruption as a composite variable termed bleeding. Model 1 contains around 30 variables which may not be easily obtainable.

4.12.2 Model 2

Pr (Respiratory disorders) = Gestational Weeks + Birth weight + Apgar 1 + Apgar 5 + Delivery Mode + Labour + **Hypertensive Disorders of Pregnancy** + Chorioamnionitis + Oligohydramnios + Polyhydramnios + Smoking + Drugs + Alcohol + Diabetes + **Bleeding** + Arterial pH + Arterial Base Excess + Fever + Meconium + Gender
+ Maternal Age

Model 2 was essentially the same as model 1 in that all continuous variables were assumed to be linearly related with the log odds of respiratory disorders and were thus left unmodified. The only important change was the inclusion of two composite variables, one for hypertensive disorders of pregnancy and the other for bleeding. The c-index was 0.868. There is little evidence of substantial gain or loss of predictive ability associated with this grouping. Including hypertensive disorders of pregnancy, a composite of PIH chronic hypertension, and hypertension complications led to a statistically insignificant result. The composite variable bleeding, also failed to achieve statistical significance at α=0.05. Therefore the grouping was maintained to remain consistent with the literature and to simplify use of the final model. Overall, statistically significant predictors of respiratory disorders included gestational age, birthweight, absence of labour, mode of delivery, chorioamnionitis, fever, Apgar scores at 1 and 5 minutes, arterial base excess and male gender.

4.12.3 Model 3

Pr (Respiratory disorders) = **Gestational Weeks_categorized** + **Birth weight_categorized** + Apgar 1 + Apgar 5 + Delivery Mode + Labour + Hypertensive Disorders of Pregnancy + Chorioamnionitis + Oligohydramnios + Polyhydramnios + Smoking + Drugs + Alcohol + Diabetes + Bleeding + Arterial pH + Arterial Base Excess + Fever + Meconium + Gender

+ Maternal Age_categorized

Model 3 was constructed in an attempt to relax linearity assumptions associated with a number of continuous predictors including gestational age, birth weight, and maternal age. Gestational age was categorized using dummy variables for 34,35, 36 and ≥37 weeks, assuming homogeneity within each category. The term(≥37 weeks) group served as the reference. Birth weight was categorized into quintiles and maternal age was split into three groups <20, 20-34 and ≥35 years of age. The middle group served as the comparator in both sets of dummy variables. Statistically significant predictors of respiratory disorders included birth at 34 vs ≥37 weeks gestation, birth at 35 vs ≥37 weeks gestation, (not for 36 vs ≥37 weeks gestation), birthweight category 1 (<10%ile), absence of labour, chorioamnionitis, intrapartum fever, APGAR scores at 1 and 5 minutes, arterial base excess and male gender. The c-index for Model 3 was 0.866.

4.12.4 Model 4

Pr (Respiratory disorders) = **Gestational Weeks_lptvsterm**_categorized +
Birth weight_categorized + Apgar 1 + Apgar 5 + Delivery Mode + Labour +
Hypertensive Disorders of Pregnancy + Chorioamnionitis + Oligohydramnios +
Polyhydramnios + Smoking + Drugs + Alcohol + Diabetes + Bleeding + Arterial pH
+ Arterial Base Excess + Fever + Meconium + Gender
+ Maternal Age_categorized

A 4-fold difference in the frequency of respiratory distress for infants born at both 37 and 41 weeks gestation was observed compared to infants born at 39 weeks, thus assuming births between 37 and 41 weeks is a homogeneous group may be inappropriate. However in the interest of simplicity, the predictive ability of making this assumption was tested in Model 4. The c-index was 0.858 and statistically significant predictors or respiratory disorders included birth at 34 and 35 weeks gestation, birthweight in the bottom 10^{th} percentile, absence of labour, cesearean

section, chorioamnionitis, intrapartum fever, lower Apgar scores at 1 and 5 minutes, arterial base excess, and male gender.

Summary of Models 1 to 4

Gestational age, cesearean section, APGAR scores at 1 and 5 minutes, arterial base excess, chorioamnionitis, intrapartum fever, male gender and absence of labour were statistically significant predictors across models 1 to 4 and may be included in models generated based on statistically significant p-values.

4.12.5 Model 5

Pr (Respiratory disorders) = Gestational Weeks_lptvsterm_categorized +
Birth weight_categorized + Apgar 1 + Apgar 5 + Delivery Mode + Labour +
Hypertensive Disorders of Pregnancy + Chorioamnionitis + Oligohydramnios +
Polyhydramnios + Smoking + Drugs + Alcohol + Diabetes + Bleeding + Arterial pH
+ Arterial Base Excess + Fever + Meconium + Gender
+ Maternal Age_categorized + **INTERACTIONS**

Model 5 included the same dummy variables as model 4, but built upon model 4 by adding all significant interactions. Three interactions with gender were modeled and 9 interactions with gestational age were modeled. Accordingly all regression coefficients incorporating these variables no longer maintain their usual interpretation. Only variables that were part of an interaction term reached statistical significance and interpretation of regression coefficients may not provide relevant information. The c-index was 0.867 for Model 5.

4.12.6 Model 6

Model 6 =lrm(resprob ~ **rcs**(GESTWK, 5) + hdp + PROM + CHORIO +
bleeding + MECON + OLIGO + HYDRAM + FEVER + SMOKE + DELIV +
rcs(BIRTHWT, 3) + SEX + APGAR1 + APGAR2 + **rcs**(ARTPH, 3) +
rcs(ARTBE, 3) + mage + labour,)

As mentioned in the construction of model 4, assuming births ≥37 weeks gestation is a homogenous group may be ill advised. Accordingly, restricted cubic splines were used instead to relax linearity assumptions for continuous variables including gestational weeks (5 knots), birth weight (3 knots), arterial pH (3 knots), and arterial base excess (3 knots). R could not obtain 3 knots for APGAR scores at 1 and 5 minutes and maternal age was found to have better fit without restricted cubic splines. Statistically significant predictors of respiratory disorders included gestational weeks, chorioamnionitis, intrapartum fever, cesearean section, birth weight, male gender, Apgar scores at 1 and 5 minutes, arterial base excess and absence of labour. The c-index was 0.868.

4.12.7 Model 7

Model 6 =lrm(resprob ~ rcs(GESTWK, 5) + hdp + PROM + CHORIO +
bleeding + MECON + OLIGO + HYDRAM + FEVER + SMOKE + DELIV +
rcs(BIRTHWT, 3) + SEX + APGAR1 + APGAR2 + rcs(ARTPH, 3) +
rcs(ARTBE, 3) + rcs(mage, 3) + labour,) +**INTERACTIONS**

Model 7 applied restricted cubic splines to continuous variables, but also added interaction terms. Since restricted cubic splines use up 2 to 4 degrees of freedom for 3 and 5 knots respectively, only highly plausible biological interactions were used. Also, interactions were only used if model convergence was achieved. Accordingly, model 7 fit interactions between gestational weeks and delivery, fever, hypertensive

disorders of pregnancy and gender. The c-index for this model was 0.871. This was known as the full model.

4.12.8 Model 8

In an effort to generate a more simplified model, reverse stepwise logistic regression was used with a stay level significance of 0.5. This was done in an effort to capture any variables that were at least mildly or moderately predictive of respiratory disorders. Three of 24 variables, PROM, polyhydramnios and alcohol use during pregnancy were eliminated. The c-index for this model was 0.851.

4.12.9 Model 9

Further efforts to simplify the model to fewer variables with similar predictive ability were pursued by backwards elimination using Akaike's Information Criterion. Eight variables were retained including gestational weeks, birthweight, chorioamnionitis, intrapartum fever, mode of delivery, gender and APGAR scores at 1 and 5 minutes. The c-index for Model 9 was 0.849.

4.12.10 Model 10

In an effort to maximize predictive ability based on factors other than p-values, the top 8 variables with the highest individual predictive ability (based on the c-indexes and Dxy's in Table 16) were used. The c-index for a model including gestational age, Apgar at 1 and 5 minutes, mode of delivery, presence or absence of labour, gender, birth weight and hypertensive disorders of pregnancy was 0.859. In this model gestational age, Apgar scores at 1 and 5 minutes, mode of delivery and gender were statistically significant predictors.

4.13 Disclaimer on p-values

Admittedly, a discussion of p values is in a sense arbitrary, however at the very least it provides a statistical, quantitative and probabilistic way of differentiating the results. The point estimate and width of the confidence intervals obtained may be more informative in gaining a sense of both the directional predictive effects of each predictor as well as the degree of accuracy with which these parameters are estimated. Similarly, it may be ill advised to compare models based on c-indexes, as the c-index may not detect small differences in predictive ability. Instead models should be appraised wholistically based on their utility, c-index, calibration slope and calibration intercept.

4.14 Validation and Nomogram Prediction of Respiratory disorders

Figure 5 shows the calibration plot for the final model. Differences in predicted and actual risks differed as evidenced by the graph. Figure 6 and 7 show the nomograms based on model 9 and 10. The c-index for these models were 0.851 and 0.857 for models 9 and 10 respectively. Model validation indicated that the degree of optimism was trivial with essentially no change between the c-index based on the original data set and that based on the 1000 fold bootstrap validation. Model calibration was excellent based on 1000 fold bootstrap validation, (even after) accounting for optimism.

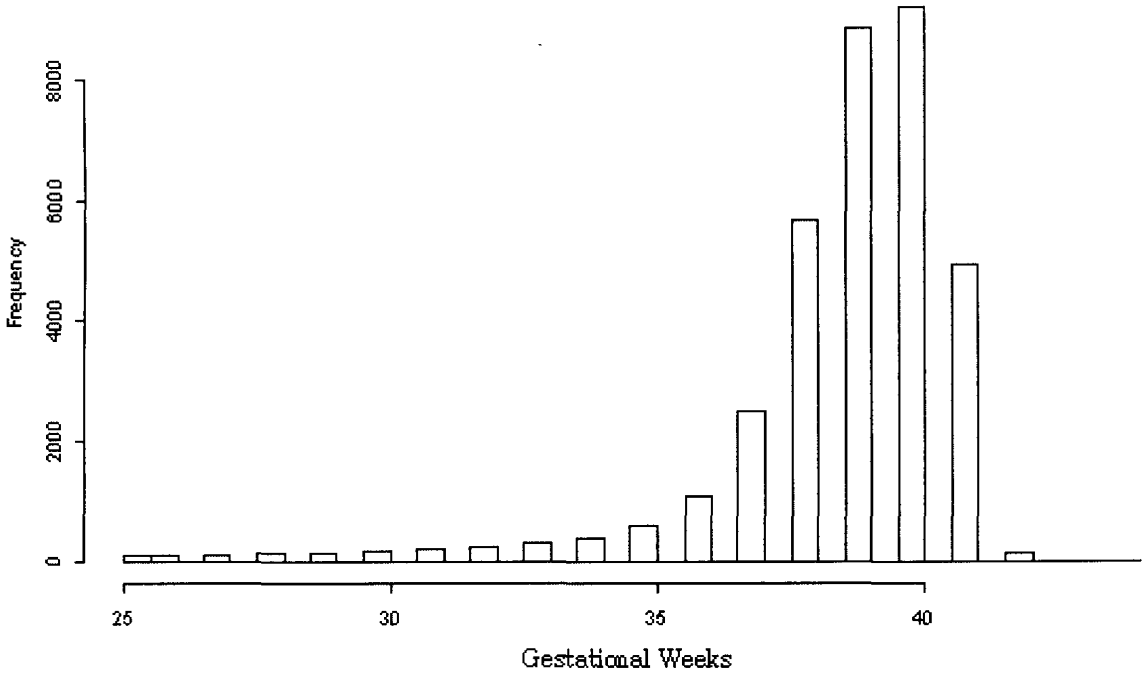

Figure 1. Frequency distribution of gestational age for all singleton births at St Joseph' Health Care London Ontario between January 31, 1996 and December 31, 2006, n=34 714.

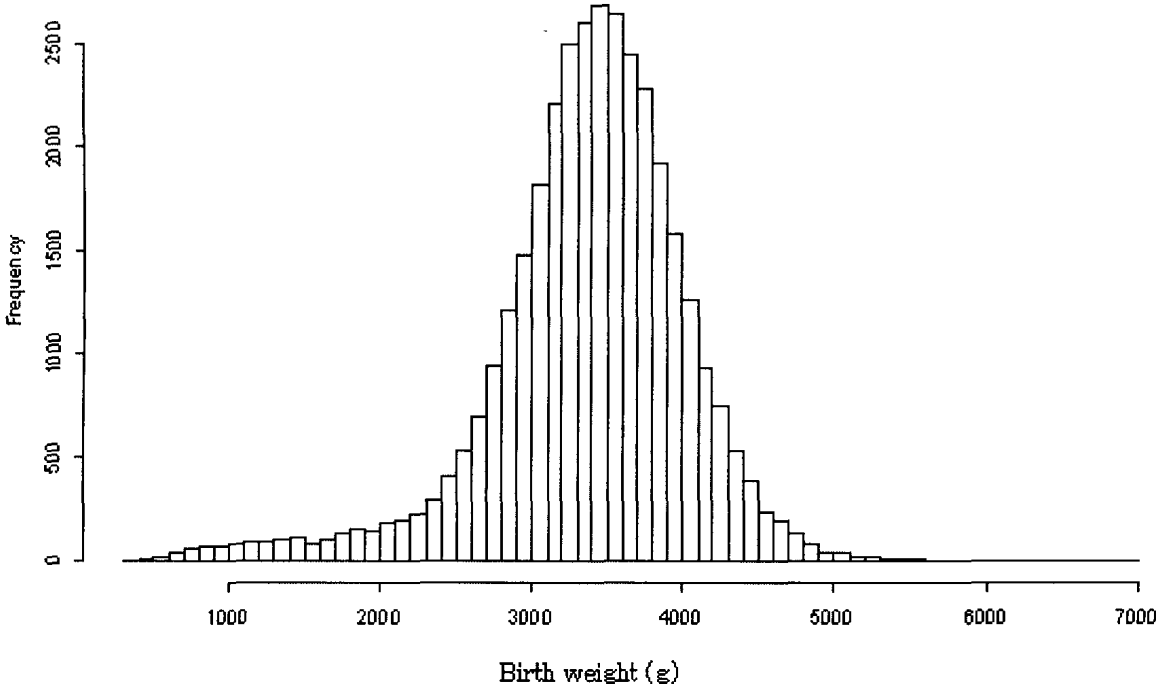

Figure 2. Frequency distribution of birth weight for all singleton births at St Joseph' Health Care London Ontario between January 31, 1996 and December 31, 2006, n=34 714.

Table 2. Mean, minimum and maximum birth weights (in grams) stratified by weeks gestation for a cohort of infants from St. Joseph's Health Care London born between January 31, 1996 and December 31, 2006. The study population excludes all congenital anomalies and births before 33 weeks gestation. (n=29531)

Gestational Age	n	Mean Birthweight (g)	Standard Deviation	Minimum Birthweight (g)	Maximum Birthweight (g)
34	325	2375.53	328.49	1575	4415
35	517	2595.64	368.42	1790	4156
36	987	2853.25	373.26	2030	4490
≥37	27702	3499.79	418.19	2275	6915
Total	29531				

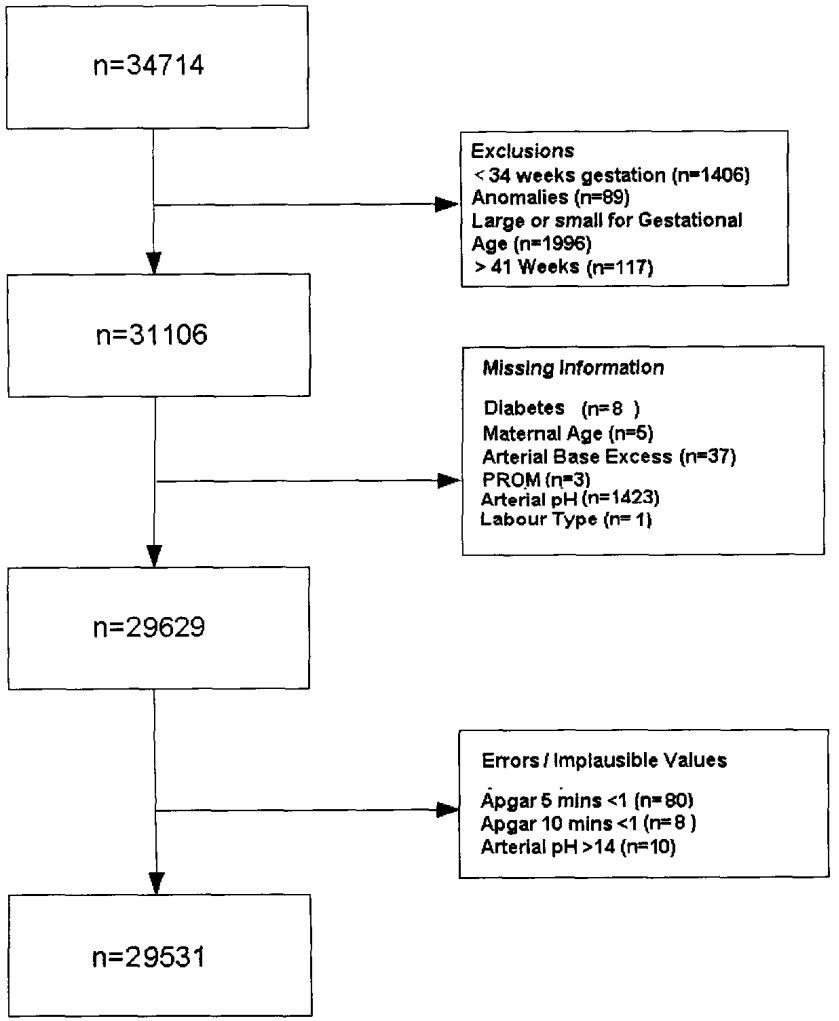

Figure 3. Flow chart illustrating the process by which the study population was obtained using inclusion/exclusion criteria and deleting missing or biologically implausible values

Table 3. Gender frequencies and percentages for a cohort of infants from St. Joseph's Health Care London born between January 31, 1996 and December 31, 2006 stratified by weeks gestation. (n=29531)

Gender	**34 weeks**	**35 weeks**	**36 weeks**	**≥37 weeks**
Female	141 (43.38)	215 (41.59)	456 (46.20)	13546 (48.90)
Male	184 (56.62)	302 (58.41)	531 (53.80)	14156 (51.10)
Total	325	517	987	27702

Table 4. Frequency of Labour (Spontaneous and Induced Labour grouped as "Labour") compared to No Labour (cesearean section without labour) and delivery types stratified by gestational weeks. (n=29531)

Labour/Delivery Type	**34 weeks n (%) n=325**	**35 weeks n (%) n=517**	**36 weeks n (%) n=987**	**≥37 weeks n (%) n=27702**
Labour Type				
Labour				
Spontaneous onset	240(71.85)	325 (62.86)	463 (47.01)	14 409 (52.01)
Induction	60 (18.96)	135 (26.11)	433 (43.96)	11 570 (41.77)
No Labour				
Cesearean Section	25 (7.69)	57 (11.03)	89 (4.69)	1723 (6.22)
Labour Type				
Labour	300 (92.31)	460 (88.97)	896 (90.96)	25 979 (93.78)
No Labour	25 (7.69)	57 (11.03)	89 (9.04)	1723 (6.22)
Delivery Mode				
Vaginal Delivery	242 (74.46)	374 (72.34)	774 (78.58)	22 700 (81.94)
Cesarean Section	83 (25.54)	143 (27.66)	211 (21.42)	5002 (18.06)

Table 5. Means and frequencies for maternal obstetrical characteristics for a cohort of infants from St. Joseph's Health Care London, Ontario born between January 1996 and December 2006, (n=29531)

Maternal Characteristic	**34 weeks** **n=325**	**35 weeks** **n=517**	**36 weeks** **n=987**	**≥37 weeks** **n=27702**
Mean Maternal Age(years)	28.9	29.32	29.67	29.74
Mean Labour Duration (hours)	6.30	5.90	6.16	8.14
Chronic Hypertension				
Absent	315 (96.92)	495 (95.74)	960 (97.26)	27365 (98.78)
Present	10 (3.08)	22 (4.26)	27 (2.74)	337 (1.22)
Chorioamnionitis				
Absent	305 (93.85)	505 (97.68)	979 (99.19)	27503 (99.28)
Present	20 (6.15)	12 (2.32)	8 (0.81)	199 (0.72)
Diabetes				
Absent	303 (99.23)	470 (90.91)	907(91.89)	26519 (95.73)
Present	22 (6.77)	47 (9.09)	80 (9.54)	1183 (4.27)
Bleeding				
Absent	256 (78.77)	421 81.43	819 (82.98)	25557 (92.26)
Present	59 (21.23)	96 (18.57)	168 (17.02)	2145 (7.74)

PROM				
Absent	255 (78.46)	424 (82.01)	900 (91.19)	27 371 (98.81)
Present	70 (21.54)	93 (17.99)	87 (8.81)	331 (1.19)
PIH				
Absent	266 (81.85)	410 (79.30)	833 (84.40)	24890 (89.85)
Present	59 (18.15)	107 (20.70)	154 (15.60)	2812 (10.15)
Meconium				
Absent	310 (95.38)	496 (95.54)	960 (97.26)	23431 (84.58)
Present	15 (4.62)	21 (4.06)	27 (2.74)	4271 (15.42)
Alcohol				
Absent	322 (99.08)	513 (99.23)	980 (99.29)	27 455 (99.12)
Present	3 (0.012)	4 (0.77)	7 (0.71)	247 (0.89)
Drugs				
Absent	317 97.54	496 95.94	966 (97.87)	27106 (97.85)
Present	8 2.46	21 4.06	21 (2.13)	596 (2.15)
Smoke				
Absent	281 86.46	439 84.91	856 (86.73)	24871 (89.78)
Present	44 13.54	78 15.09	131 (13.27)	2831 (10.22)

Oligohydramnios				
Absent	315 (96.92)	486 (94.00)	944 (95.64)	27 074 (97.73)
Present	10 (3.08)	31 (6.00)	43 (4.36)	628 (2.27)
Polyhydramnios				
Absent	320 (98.46)	506 (97.87)	968 (98.07)	27 466 (99.15)
Present	5 (1.54)	11 92.13)	19 (1.93)	236 (0.85)
Intrapartum Fever				
Absent	318 (97.85)	513 (99.23)	975 (98.78)	26 898 (97.10)
Present	7 (2.15)	4 (0.77)	12 (1.22)	804 (2.90)

Table 6. Newborn characteristics for the study population at St Joseph's Health Care London born between January 1996 and December 2006 stratified by gestational age. (n=29531)

Neonatal Characteristic	**34 weeks** **n=325**	**35 weeks** **n=517**	**36 weeks** **n=987**	**≥37 weeks** **n=27702**
1 minute APGAR mean (median)	7.17 (8)	7.5 (8)	7.82 (8)	8.14 (9)
5 minute APGAR mean (median)	8.37 (9.0)	8.6 (9)	8.78 (9)	8.94 (9)
Arterial pH	7.35	7.26	7.26	7.28
Arterial PO2	18.41	18.31	17.80	17.05
Arterial PCO2	52.37	52.63	52.80	53.81
Venous pH	7.32	7.33	7.33	7.34
Venous PO2	27.04	27.27	27.83	28.33
Venous PCO2	43.32	43.01	42.08	41.21
Venous base excess	-4.02	-3.94	-3.91	-4.26

Table 7. Mortality among term and late preterm infants including and excluding anomalies for the study population at St Joseph's Health Care London born between January 1996 and December 2006 and stratifying by gestational age.

	34 weeks	**35 weeks**	**36 weeks**	**≥ 37 weeks**
Including Anomalies n=34 714	n=387	n=587	n=1099	n=31235
Alive	378 (97.67)	582 (99.15)	1093 (99.45)	31176 (99.81)
Stillbirth	4 (1.03)	5 (0)	5 (0.45)	49 (0.16)
Early Neonatal Death	4 (1.03)	0 (0)	0 (0)	9 (0.03)
Death after 28 days of Age	1 (0.26)	0 (0)	1 (0.09)	1 (0)
Excluding Anomalies	n=386	n=586	n=1094	n=31159
Alive	378 (97.93)	581 (99.15)	1088 (99.45)	31103 (99.82)
Stillbirth	4 (1.04)	5 (0.85)	5 (0.46)	47 (0.15)
Early Neonatal Death	3	0 (0)	0 (0)	9 (0.03)
Death after 28 days of age	1 (0.26)	0 (0)	1 (0.09)	0 (0)

***There were no late neonatal deaths (7 to 28 days of age)**

Table 8. Unadjusted Risk Ratios and their respective 95% confidence intervals for a number neonatal morbidities for the study population at St Joseph's Health Care London born between January 1996 and December 2006 stratified by gestational age. Morbidity frequencies at 34, 35 and 36 weeks are compared to morbidity frequencies among term infants born at 37 weeks gestation or later.

Morbidity	**34 weeks gestation** Present Absent **Risk Ratio (95% Confidence Interval)**	**35 weeks gestation** Present Absent **Risk Ratio (95% Confidence Interval)**	**36 weeks gestation** Present Absent **Risk Ratio (95% Confidence Interval)**
RDS	44 (13.54) 281 (86.46) **96.16 (63.38 to 145.91)**	32 (6.19) 485 (93.81) **43.96 (27.77 to 69.60)**	22 (2.23) 965 (97.77) **15.83 (9.42 to 26.60)**
Transient Tachypnea	72 (22.15) 253 (77.85) **23.16 (18.28 to 29.34)**	54 (10.44) 463 (89.56) **10.92 (8.26 to 14.44)**	55 (5.57) 932 (94.43) **5.83 (4.39 to 7.73)**
Apnea/Bradycardia	21 (6.46) 304 (93.54)	14 (2.71) 503 (97.29)	9 (0.91) 978 (99.09)

	77.83(43.51 to 139.19)	**32.62 (16.88 to 63.02)**	**10.98 (5.10 to 23.67)**
Patent Ductos Ateriosus	3 (0.92) 322 (99.08) **7.99 (2.46 to 25.96)**	4 (0.77) 513 (99.23) **6.70 (2.38 to 18.87)**	6 (0.61) 981 (99.39) 5.26 (2.21 to 12.56)
Necrotizing Enterocolitis	4 (1.23) 321 (98.77) **48.71(14.33 to 165.57)**	4 (0.77) 513 (99.23) **30.62 (8.99 to 104.27)**	3 (0.30) 984 (99.70) **12.03 (3.12 to 46.47)**
Meconium	8 (2.46) 317 (97.54) **2.87 (1.43 to 5.75)**	4 (0.77) 513 (99.23) **0.90 (0.34 to 2.41)**	4 (0.41) 983 (99.59) **0.47 (0.18 to 1.26)**
Sepsis	5 (1.54) 320 (98.46) **35.52(12.58 to 100.23)**	7 (1.35) 510 (98.65) **31.26 (12.36 to 79.07)**	3 (0.30) 984 (99.70) **7.02 (1.98 to 24.83)**
Intracranial hemorrhage	109 (33.54) 216 (66.46) **0.35 (0.30 to 0.41)**	191 (36.94) 326 (63.06) **0.66 (0.62 to 0.70)**	153 (15.50) 834 (84.50) **0.88 (0.86 to 091)**

Table 9. Unadjusted Risk Ratios and their respective 95% confidence intervals for infants requiring interventions in the Neonatal Intensive Care Unit for the study population at St Joseph's Health Care London born between January 1996 and December 2006 stratified by gestational age. Morbidity frequencies at 34, 35 and 36 weeks are compared to morbidity frequencies among term infants born at 37 weeks gestation or later.

Intervention	**34 weeks gestation** Present Absent **Risk Ratio (95% Confidence Interval)**	**35 weeks gestation** Present Absent **Risk Ratio (95% Confidence Interval)**	**36 weeks gestation** Present Absent **Risk Ratio (95% Confidence Interval)**
Endotracheal Tube	9 (2.77) 316 (97.23) **7.99 (4.07 to 15.69)**	9 (1.74) 508 (98.26) **5.02 (2.55 to 9.89)**	8 (0.81) 979 (99.19) **2.34 (1.14 to 4.80)**
CPAP*	32 (9.85) 293 (90.15) **44.71 (29.57 to 67.62)**	29 (5.61) 488 (94.39) **25.47 (16.51 to 39.29)**	24 (2.43) 963 (97.57) **11.04 (6.92 to 17.63)**
Supplemental Oxygen	96 (29.54) 229(70.46) **20.98 (17.27 to 25.49)**	84 (16.25) 433 (83.75) **11.54 (9.27 to 14.37)**	70 (7.09) 917 (92.91) **5.04 (3.94 to 6.45)**

Surfactant	25 (7.69) 300 (92.31) **57.59 (35.09 to 94.53)**	15 (2.90) 502 (97.10) **21.72 (12.00 to 39.33)**	17 (1.72) 90 (98.28) **12.90 (7.29 to 22.82)**
Mechanical Ventilation	46 (14.15) 279 (85.85) **34.09 (24.66 to 47.14)**	33 (6.38) 484 (93.62) **15.38 (10.54 to 22.42)**	35 (3.55) 952 (96.45) **8.54 (5.88 to 12.40)**
Surgery	20 (6.15) 305 (93.85) **19.82 (12.34 to 31.85)**	14 (2.71) 503 (97.29) **8.72 (4.99 to 15.24)**	15 (1.52) 972 (98.48) **4.90 (2.84 to 8.44)**

*Continuous positive airway pressure

Table 10. Frequency of NICU admission for the study population at St Joseph's Health Care London born between January 1996 and December 2006 stratified by gestational age. (n=29531)

NICU Admission	34 weeks	35 weeks	36 weeks	≥37 weeks
Yes	294 (90.46)	285 (55.13)	248 (25.13)	1941 (7.01)
No	31 (9.54)	232 (44.87)	739 (74.87)	25761 (92.99)
Total	325	517	987	27702

Table 11. Intervention use in days for the study population at St Joseph's Health Care London born between January 1996 and December 2006 stratified by gestational age.

Intervention	34 weeks	35 weeks	36 weeks	≥37 weeks
Days on Oxygen	8.19 (1.37,15.00)	5.42 (1.37,9.46)	5.07(2.25,7.89)	3.17(2.50,3.84)
Days on CPAP	2.07 (1.00,3.14)	2.43(1.13,3.73)	1.67(1.30,2.04)	2.03(1.53,2.52)
Days on Ventilator	7.40 (1.42,13.87)	5.75(0.28,11.23)	4.80(2.10,7.51)	3.30(2.33,4.27)
Feed Days	4.96 (4.08,5.83)	4.72(3.87,5.56)	4.52(3.39,5.65)	2.86(2.63,3.10)
Length of Stay in the NICU (days)	12.79 (11.25,14.33)	9.28(8.16,10.41)	7.80(6.61,9.00)	4.52(4.24,4.81)

Table 12. The frequency of neonatal sepsis for the study population at St Joseph's Health Care London born between January 1996 and December 2006 stratified by gestational age. (n=29531)

Neonatal Sepsis	34 weeks gestation	35 weeks gestation	36 weeks gestation	≥37 weeks gestation
Present	10 (3.08)	10 (1.93)	5 (0.51)	27 (0.10)
Absent	316 (96.92)	507 (98.07)	982 (99.49)	27675 (99.90)

Table 13. Results of univariable logistic regression for the individual predictors regressed on respiratory disorders for the study population at St Joseph's Health Care London born between January 1996 and December 2006 stratified by gestational age.

Predictor	Odds Ratio	95% Wald Confidence Limits
Sex (Male to Female)	1.843	(1.551, 2.190)
Hypertension	1.425	(0.778, 2.610)
Premature Rupture of Membranes	4.534	(3.316, 6.201)
Maternal Age	0.988	(0.974, 1.003)
Previous Cesearean Section	1.212	(0.951, 1.544)
Maternal Bleeding	2.088	(1.665, 2.619)
Maternal Diabetes	1.193	(0.862, 1.651)
Type of Delivery	2.549	(2.147, 3.025)
HDP*	1.808	(1.456, 2.246)
Smoking during pregnancy	1.213	(0.945, 1.557)
Meconium	0.796	(0.62, 1.022)
Oligohydramnios	1.921	(1.287, 2.867)
Polyhydramnios	2.534	(1.448, 4.467)
Fever	2.324	(1.647, 3.280)
Alcohol use during pregnancy	1.178	(0.522, 2.658)
Drugs	1.123	(0.657, 1.919)
Apgar at 1 minute	0.713	(0.691, 0.735)
Apgar at 5 minutes	0.478	(0.447, 0.512)
Arterial pH	0.152	(0.047, 0.490)
Arterial base excess	0.761	(0.737, 0.984)

*HDP=Hypertensive Disorders of Pregnancy

Birth weight quintile	Odds Ratio	95% Wald Confidence Limits
1	0.131	(0.108,0.159)
2	0.805	(0.607,1.067)
4	1.182	(0.853,1.636)
5	0.954	(0.671,1.356)

Labour Type	Odds Ratio	95% Wald Confidence Limits
Induction vs Spontaneous	1.069	(0.895,2.517)
C-Section vs Spontaneous	2.517	(1.957,3.238)

Gestational Weeks	Odds Ratio	95% Wald Confidence Limits
34 vs ≥37 weeks	49.489	(38.419,63.749)
35 vs ≥37 weeks	17.544	(13.551,22.714)
36 vs ≥37 weeks	7.455	(5.751,9.665)

Maternal Age	Odds Ratio	95% Wald Confidence Limits
<20 vs 20to34 yrs	1.272	(0.870,1.861)
>35 vs 20to34 yrs	1.074	(0.874,1.320)

PROM	Odds Ratio	95% Wald Confidence Limits
1-5 hrs vs No PROM	1.039	(0.748 to 1.444)

6-24 hrs vs No PROM	1.654	(1.291 to 2.119)
>24 hrs vs No PROM	4.948	(3.555 to 6.886)

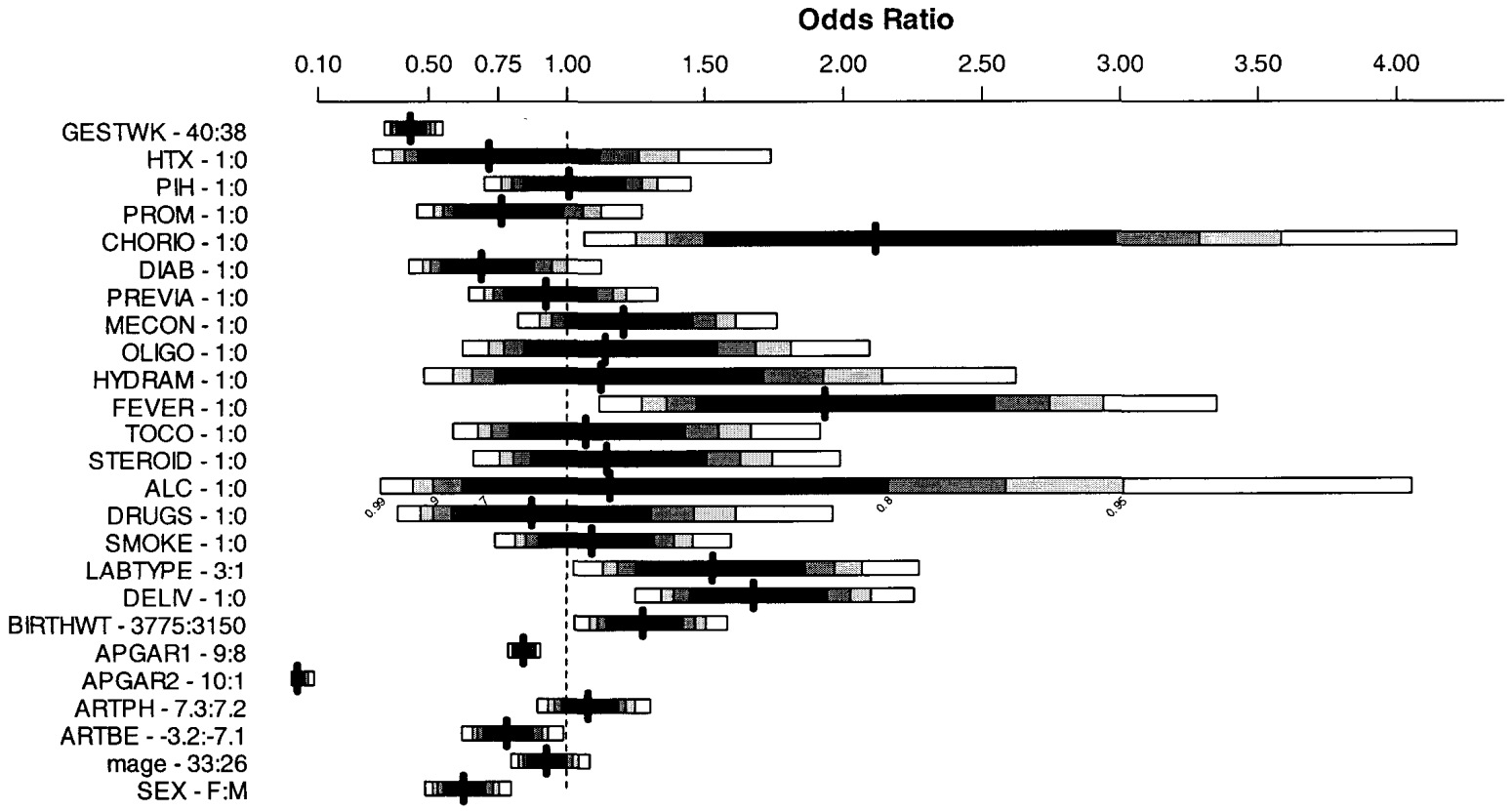

Figure 4. Odds ratios and confidence intervals for Model 1, using quartiles of gestational age, birth weight, Apgar scores at 1 and 5 minutes, arterial pH, arterial base excess, and maternal age for assessing their effects on the odds of respiratory disorders.

Table 14. Respiratory disorders for the study population at St Joseph's Health Care London born between January 1996 and December 2006 stratified by gestational weeks.

Gestational Weeks	Respiratory disorders Absent	Respiratory disorders Present
34	228 (70.15)	97 (29.85)
35	449 (86.85)	68 (13.15)
36	916 (92.81)	71 (7.19)
37	2115 (96.84)	69 (3.16)
38	4979 (98.89)	56 (1.11)
39	7780 (99.27)	57 (0.73)
40	8163 (99.17)	68 (0.83)
41	4378 (99.16)	37 (0.84)
42	113 (96.58)	4 (3.42)
43	3 (100)	0 (0)
44	1 (100)	0 (0)

Table 15. C-indexes and Somers' D for all maternal and neonatal predictors obtained by univariable logistic regression of respiratory disorders for the study population at St Joseph's Health Care London born between January 1996 and December 2006 stratified by gestational age. Values are arranged according by decreasing predictive discrimination.

Maternal or Neonatal Characteristic	C - index	Somers' Dxy
Gestational age	0.759	0.518
Apgar 1	0.729	0.458
Birth weight	0.692	0.385
Apgar 2	0.689	0.378
Mode of Delivery	0.582	0.164
Gender	0.571	0.141
Hypertensive Disorders of Pregnancy	0.539	0.077
Presence of Labour	0.538	0.076
Arterial base excess	0.538	0.075
Arterial pH	0.535	0.071
Premature Rupture of Membranes	0.531	0.061
Maternal age	0.525	0.049
Chorioamnionitis	0.521	0.042
Intrapartum Fever	0.519	0.037
Smoking during pregnancy	0.514	0.027
Meconium	0.513	0.026
Bleeding	0.512	0.024
Oligohydramnios	0.510	0.020
Maternal Diabetes	0.507	0.015
Oligohydramnios	0.505	0.010
Drug use during pregnancy	0.502	0.003
Alcohol use during pregnancy	0.501	0.003

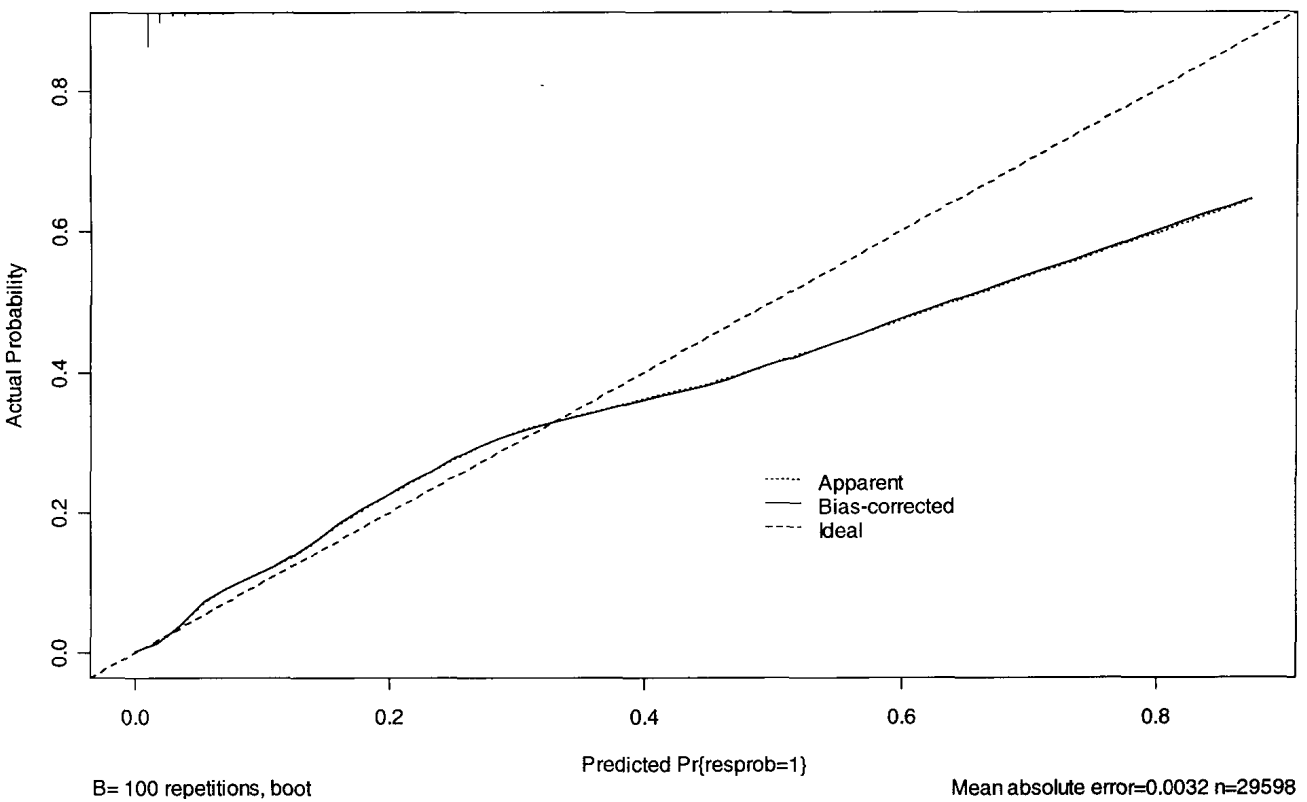

Figure 5. Calibration curve for predicting respiratory problems in infants born ≥34 weeks. On the calibration curve, x-axis is the nomogram predicted probability of respiratory problems and the y-axis is the observed probability of respiratory problems.

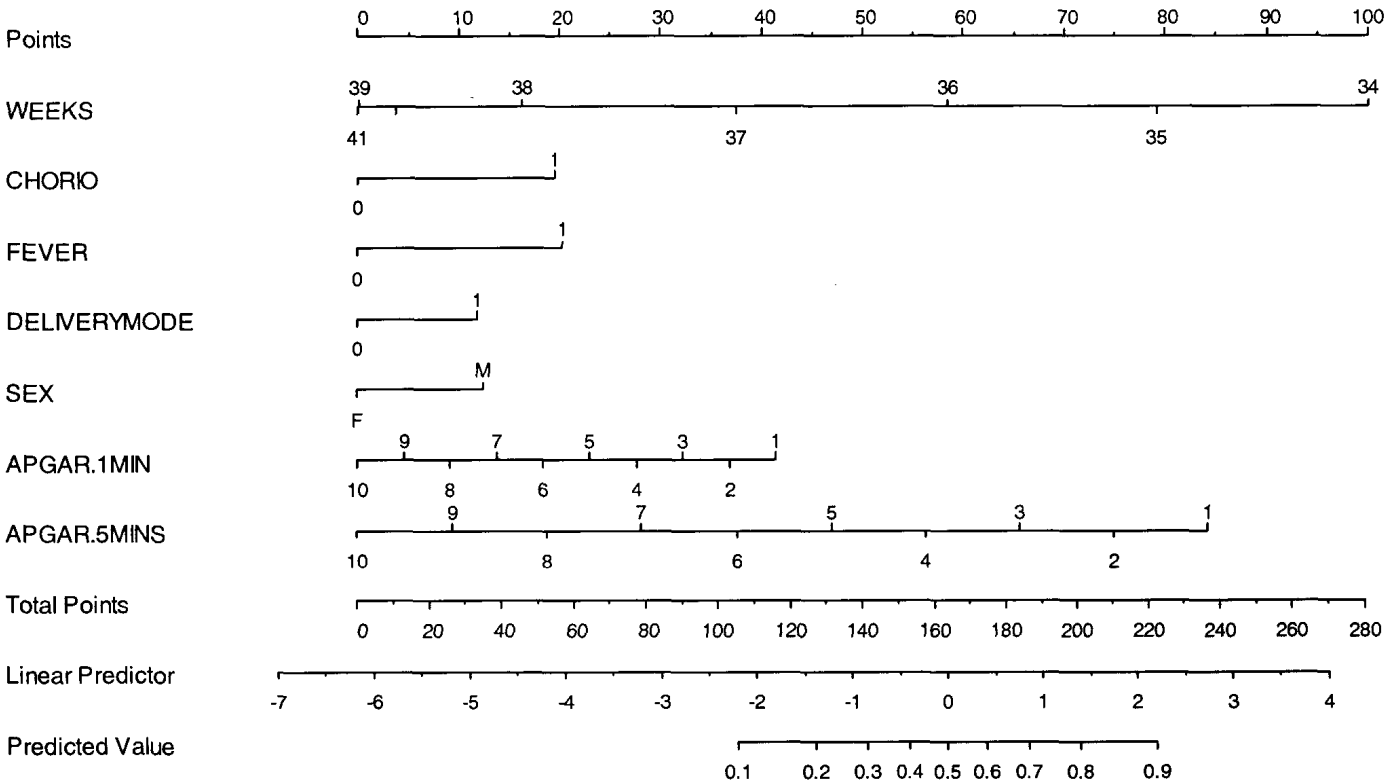

Figure 6. Nomogram for predicting respiratory disorders for infants born between ≥34 and ≤41 weeks gestation using Model 9. Instructions for users: For each predictor, draw a straight line up to the points axis to determine the number of points towards respiratory disorders each predictor contributes. Sum the points earned from each predictor to obtain a total number of points. Locate the total obtained on the Total Points Axis. Connect a straight line down from the Total Points axis to the Predicted Value axis to ascertain the infant's risk of developing respiratory disorders.

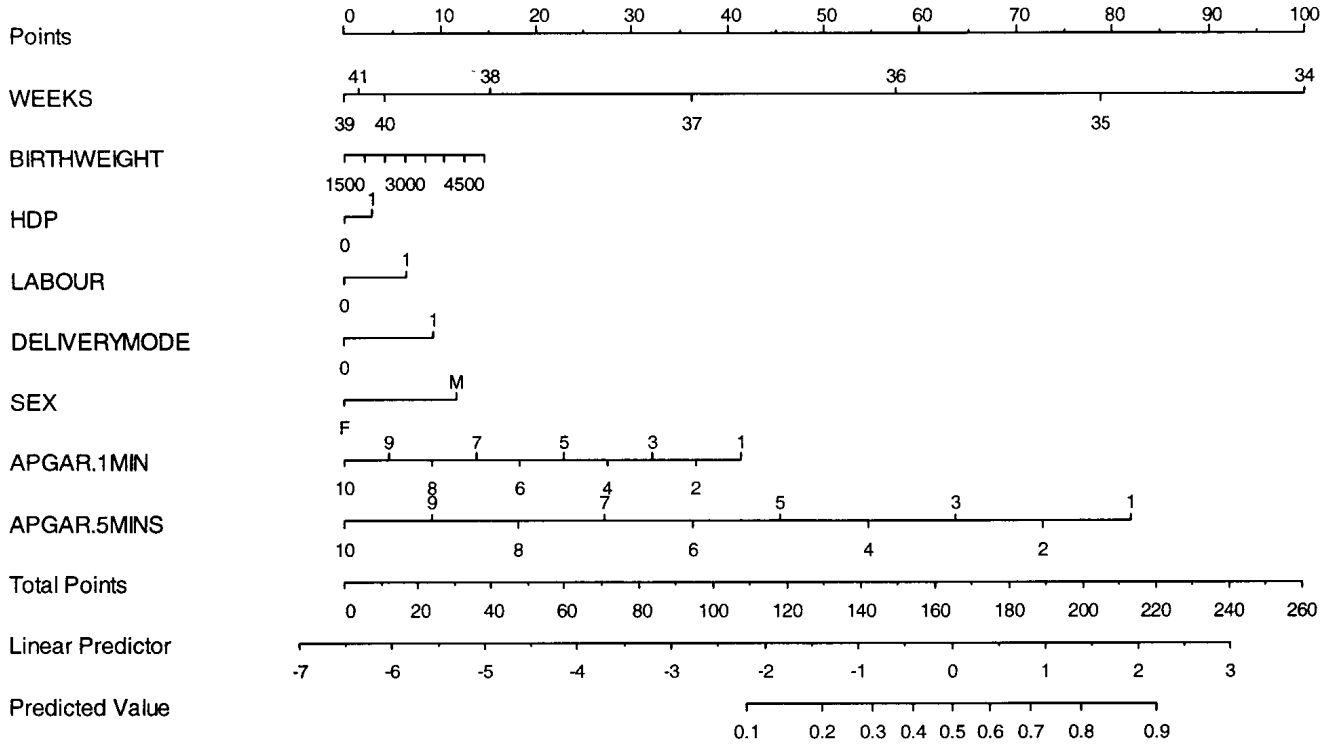

Figure 7. Nomogram for predicting respiratory disorders for infants born between ≥34 and ≤41 weeks gestation using Model 10. Instructions for users: For each predictor, draw a straight line up to the points axis to determine the number of points towards respiratory disorders each predictor contributes. Sum the points earned from each predictor to obtain a total number of points. Locate the total obtained on the Total Points Axis. Connect a straight line down from the Total Points axis to the Predicted Value axis to ascertain the infant's risk of developing respiratory disorders.

Chapter 5: Discussion

5.1 The Predictive Model

In an effort to differentiate high from low risk late preterm infants in order to intervene earlier, this study has focused on developing a tool that will enhance a neonatalogist's ability to predict an individual late preterm infant's risk of respiratory disorders. Considering that neonatologists have an obligation to provide the best possible care for each infant as the consequences of their care have implications that span entire life times, this tool would be highly beneficial for a number of reasons. In the short term this tool will assist health care providers in better preparing, planning and treating late preterm infants immediately following birth. As well, this tool may be used to counsel expectant mothers, improve knowledge of maternal care and guide non-emergency obstetric intervention decisions. Importantly this tool could assist obstetricians in deciding between delaying and delivering by helping identify low and high risk infants. In the long run, earlier interventions could prevent long-term morbidities and as a secondary societal benefit, early intervention could also limit health, education and social service spending.

5.1.1 Multivariable Discussion

5.1.1.1 The Predictive Model

Examining morbidity among term and late preterm infants in a population based cohort of 29,531 infants using both obstetrical and neonatal characteristics, an internally validated model for predicting respiratory disorders was developed. This model may be widely applicable as it makes use of easily obtainable and routinely collected obstetrical and neonatal characteristics. This model is strong in that it employed a bootstrapping validation process so as to achieve a nearly unbiased estimate of internal validity. This model is also strong in that restricted cubic splines are used to allow for non-linear associations between predictors and respiratory disorders.

5.1.1.2 Predictive Ability

The c-index for the full model was 0.87 indicating better than good discrimination. For those preferring a rank correlation coefficient ranging from -1 to +1, Somers' Dxy index was 0.75. A more honest estimate of Somers' D was obtained by validating the model using bootstrapping, yielding a nearly unbiased estimate of predictive ability of 0.74. The calibration slope was 0.96 and the intercept 0.003. As mentioned, perfect calibration is indicated by a calibration slope of 1 and an intercept equal to 0. Although very close to 1 and 0, a calibration slope less than 1 indicates that the regression coefficients were too high, resulting in low predictions being slightly too low and high predictions that are slightly too high. This relationship is evidenced by the calibration plot.

The full model with the greatest predictive ability includes continuous predictors modeled using restricted cubic splines, grouped variables for hypertensive disorders of pregnancy, maternal bleeding, diabetes and labour, as well 2 interaction terms with sex and 5 interaction terms with gestational age. The use of restricted cubic splines and interaction terms likely makes this model less subject to inaccuracies associated with violated assumptions. This high degree of accuracy however comes at a price, as interpreting regression coefficients and odds ratios from this model may be impossible. Many authors have noted that it is important to avoid stepwise procedures and to use the full model wherever possible. Generally, variable selection and univariable screening based on statistical significance may reduce predictive accuracy of the final model because the variables that remain after this process have overstated effects, and their coefficients are too high.

Predictive discrimination with just 8 variables was still better than good at 0.86. Thus, although there is some added predictive ability associated with using all variables, the reduction in predictive ability associated with the model reduced by fast backwards elimination using the AIC stopping criteria or with the 8 highest c-indexes maintains almost all of the predictive ability with about1/3 the number of variables. Furthermore, tracking down all 30 variables for one patient may be counterproductive

and not clinically useful in a busy NICU. Thus depending on one's goals, there are different models for different objectives. The full model provides more accurate estimates requiring more variables, while the reduced model provides very similar predictive ability with far fewer variables. Accordingly, the reduced model may be implemented much easier, more widely and may have potential as a similar score to the APGAR score predicting respiratory disorders at birth.

It should be noted that these data cannot predict individual outcomes but rather provide a strong internally valid estimate of the probability of respiratory disorders. It is also important to note that outcomes change over time and that outcomes may differ for a variety of reasons, including genetics[68], patient population, obstetric complications and care after discharge home. As well, since the study was conducted at a Level III NICU, the results may not apply to hospitals with lower level NICUs.

5.1.1.3 The Nomogram

The downside of employing restricted splines is that non-linear spline-based coefficients are very difficult, if not impossible to interpret and apply in a clinical setting. Accordingly, the nomogram provides a simple, effective and user-friendly way for clinicians to input predictor variables and obtain a probability of respiratory disorders for the specific infant being cared for. The majority of the variables have intuitive interpretations. For example, lower gestational weeks and male gender lead to higher points and higher risks, while higher APGAR scores are protective and result in fewer points and lower risks. The relative magnitude or impact of each variable is indicated by the width of the line representing each predictor. Gestational age for example extends across the entire point scale indicating that a birth at 34 weeks contributes the maximum number of points, whereas male gender contributes only about 10 points indicating a lower relative contribution to the risk of respiratory disorders.

5.2 Discussion of Maternal and Neonatal Predictors

5.2.1 Possible Explanations for Increased Risks Associated with Maternal and Neonatal Conditions

Shapiro-Mendoza et al[140] proposed three possible explanations for the greater risks of newborn morbidity among late preterm infants exposed to maternal conditions. Firstly, more pregnancies are occurring among older, pregnant women with chronic medical conditions. More specifically, pregnancy could worsen the medical condition leading to preterm delivery, and exposing the infant to the combined effects of the maternal condition and preterm birth. Secondly a chronic maternal condition could compromise a mother's ability to support a term pregnancy and thirdly, medications for chronic maternal conditions may worsen the pregnancy. For example, a recent study examining mother's with asthma who were taking oral steroids found that infants born to these mothers were more likely to be delivered preterm and were more likely to develop transient tachypnea of the newborn compared to mothers who did not take steroids.

PROM

This study does not provide evidence to support the notion that PROM is a significant predictor of respiratory disorders. This is consistent with other studies which report associations with placental abruption, and infections including intramniotic infections, endometrial infections and septicemia.[131] Preterm premature rupture of membranes (pPROM) is associated with preterm birth which may in turn increase an infant's risk of respiratory disorders.

Birth weight

Low birth weight, either due to preterm birth, or growth restriction has been observed to be associated with hypoglycemia, hypothermia and respiratory disorders. Similarly, infants of higher birth weights have been observed to be at a greater risk of

respiratory disorders. With the exclusion of infants born later than 42 weeks and infants who were large for gestational age, combined with the fact that many late preterm infants are relatively similar in size to term infants, there was likely few infants who were at a high risk of morbidity problems due to birth weight. The only exception may be the inclusion of infants with birth weights in the 4^{th} to 10^{th} percentile, a range which includes many intrauterine growth restricted infants. Higher rates of respiratory problems were observed among infants with birth weights less than the 10^{th} percentile for the study population, and intrauterine growth restriction may provide a potential explanation. Based on the results of this study, at least birth weight in the 4^{th} to 10^{th} percentile appears to be a statistically significant predictor of respiratory disorders.

Labour

The presence of labour is known to trigger both fetal lung clearance and surfactant production. Both factors are important in lung maturation and are protective against respiratory disorders. Thus, the observation that the presence of labour was protective is consistent with other studies.[86]

Hypertensive Disorders of Pregnancy

Hypertensive disorders of pregnancy did not appear to increase the risk of respiratory disorders. Previous studies indicate that mild hypertension leads to pregnancies with roughly average preterm birth rates and birth weights. Severe hypertension has been linked to higher risks of maternal and perinatal morbidity, higher preterm birth rates, more small for gestational age infants and higher rates of placental abruption.[154] Previous studies have not linked hypertension to respiratory disorders and some suggest it may be protective in that this disorder may provide a stressful intrauterine environment that encourages maturation. Based on the results of this study, hypertensive disorders may have some predictive ability related to respiratory disorders however further studies which can differentiate severe from mild and gestational hypertension from chronic hypertension may improve the accuracies of predictions.

Maternal Diabetes

Neonatal morbidities previously found to be associated with maternal diabetes(mellitus) include congenital anomalies, caudal regression syndrome, premature delivery, macrosomia, intrauterine growth restriction, and respiratory distress (especially before 38.5 weeks). Diabetes is believed to lead to respiratory distress by delaying production of surfactant as a consequence of hyperinsulinemia. Gestational diabetes mellitus and respiratory distress are also associated with pneumonia, hypertrophic cardiomyopathy and transient tachypnea. TTN is believed to arise from an inability to clear the diabetic lung.[148] It was thus a surprising finding that diabetes was not significantly associated with respiratory disorders. This finding may have resulted from grouping gestational and chronic diabetes or may indicate that late preterm infants represent a unique group who are less susceptible to maternal diabetes, a finding that may be worthy of further study.

Bleeding

Placenta previa, placental abruption and bleeding in general have not been reported to be associated with respiratory disorders, although they were somewhat predictive of respiratory disorders. Previous studies indicate that placenta previa is associated with preterm premature rupture of membranes (PPROM), malpresentation, fetal growth restriction, and vasa previa, while placental abruption is associated with disseminated intravascular coagulopathy and death, while vaginal bleeding is associated with PPROM.[178] There does not appear to be statistically significant evidence that bleeding during pregnancy is predictive of respiratory disorders.

Chorioamnionitis and Fever

Chorioamnionitis is a risk factor for neonatal death and disease and has been observed to be associated with PPROM, preterm labour, prolonged labour, preterm delivery, and fetal newborn infections.[157] Chorioamnionitis achieved statistical

significance in the final 8variable model indicating that it may be a strong predictor of respiratory disorders in late preterm infants. This may be an important finding, as few studies have reported chorioamnionitis as a risk factor after adjusting for gestational age. Similarly, fever is a statistically significant predictor of respiratory disorders based on the findings from this study.

Oligohydramnios

Oligohydramnios, a condition in which less amniotic fluid is present than expected for a given gestational age, is associated with chromosomal abnormalities, congenital anomalies, fetal growth restriction, fetal demise, post term pregnancy and ruptured fetal membranes.[153] Thus the finding that oligohydramnios was not significantly assoiciated with respiratory problems is consistent with previous studies.

Polyhydramnios

Polyhydramnios a condition in which too much amniotic fluid is present for a given gestational age, has been observed to be associated with an increase risk of preterm labour, PPROM, fetal malpresentation, and umbilical cord prolapse. Consistent with other studies, polyhydramnios does not appear to be highly predictive of respiratory disorders.[63]

Smoking

Smoking during pregnancy is associated with spontaneous pregnancy loss, placental abruption, PPROM, placenta previa, preterm labour and delivery, low birth weight and ectopic pregnancy. Respiratory distress has not been found to be associated with smoking, however smoking appears to lead to preterm birth which in turn increases an infants risk of respiratory disorders.[5] Smoking may have not been accurately captured in the database as there is so much potential for heterogeneity in exposure, reporting and genetic factors associated with tobacco smoke exposure.

Alcohol Use During Pregnancy

Maternal alcohol use during pregnancy is associated with growth problems, facial dysmorphia, and central nervous system abnormalities. Alcohol use was not found to be an important predictor of respiratory disorders. These findings however do not rule out the role of alcohol use in respiratory disorders as this variable was likely underreported. Furthermore, alcohol use as an all encompassing group is heterogenous and likely does not capture the variety of exposure levels inherent in this group. Further problems are associated with attempts to explain drug use as exposure is not limited to alcohol or tobacco, but rather to any illicit drugs. Different classes of drugs are associated with different outcomes, which complicates and limits interpretations and conclusions.

Mode of Delivery

The mode of delivery, ie cesearean section versus vaginal delivery served as an important predictor of respiratory disorders. Infants born via cesearean section are more likely to have missed the hormonal triggering of lung maturation that is a part of spontaneous or induced vaginal delivery. Accordingly, these infants were likely at a much higher risk of respiratory disorders, a finding that is consistent with other studies.

APGAR Scores at 1 and 5 Minutes

APGAR scores allocate points ranging from 0 to 2 for each of heart rate, respiratory effort, muscle tone, reflex, irritation and colour. Higher scores indicate more stable infants. Accordingly, the finding that lower APGAR are predictive of respiratory disorders is not surprising. Of note, some previous authors have found that APGAR scores are not predictive of respiratory distress syndrome[136].

5.3 The Importance of this Predictive Model

5.3.1 A First in the Late Preterm Literature

No previous Canadian studies have been published specifically on respiratory disorders among Late Preterm Infants. Numerous studies in the United States, have illuminated concerning trends associated with Late Preterm birth. The current study is a large, population based study and will be important in providing Canadian morbidity and mortality rates among Late Preterm Infants that will be generalizable to Level III Perinatal Units across Canada. Previous studies have described characteristics which may place late preterm infants at risk of morbidity. However this study is the first to build on these studies and take this information a step further. Our model is the first model with the capacity to take maternal and neonatal characteristics and obtain a probability specific to respiratory disorders and specific to each infant it is applied to. Although unvalidated on an external population, an honest and relatively unbiased estimate of the c-index is 0.87. This indicates very good discrimination. Together with a slope of 0.96 and an intercept of 0.001, this model is also well calibrated and indicates very little bias related to risk estimates. Accordingly this tool has the potential to be crucial in identifying infants at high and low risk of developing potentially life threatening respiratory disorders.

5.3.2 Improvements in Health Which Will Result

As mentioned, although many late preterm infants appear healthy at birth, late preterm infants are developmentally immature as compared to term infants and are at a much higher risk of mortality and morbidity. Accordingly, this study will ideally assist clinicians not only in monitoring, planning and treating late preterm infants, but also in communicating risks to family members and neonatal staff leading to more proactive, consistent and evidence-based care for this developmentally immature and vulnerable group of infants[22,27]. Furthermore, this study may provide justification for clinical trials examining the effects of emerging therapies such as 17 alpha-hydroxyprogesterone caproate which is aimed at preventing and limiting preterm birth and its potentially devastating consequences[14].

5.4 Major Findings Related to Objectives 2 and 3

5.4.1 Late Preterm Birth

As mentioned in the results, the late preterm birth rate for this study population was 6.09%. By comparison, late preterm birth rates were 4.5% and 4.9% for the two Canadian birth cohorts and 6.3% and 7.6% for two American birth cohorts analyzed by Kramer. The two Canadian cohorts were from 1985-1987 (n=692 579) and 1992-1994 (n=726 435) and excluded Ontario due to data quality issues. These findings may be important in illustrating a higher late preterm birth rate in London and/or Ontario compared to Canada as a whole. Considering Ontario is the most populated province, this finding may have important public health implications. Higher late preterm birth rates may also be due to St Joseph's status as a tertiary referral center.

5.4.2 Gender Differences

The observation that more males were born preterm is consistent with previous study findings globally. With this observation in mind, closer monitoring of male late preterm infants is warranted. Looking beyond simply late preterm birth rates, considerable differences were observed between genders on a number of other factors. Males were more likely to be admitted to the NICU, to develop respiratory distress and to stay longer in hospital. These differences in gender are believed to be the result of a female survival advantage. This advantage encompasses biological factors including a more favorable 'hormonal milieu' resulting in lower morbidity rates including chronic lung disease and intraventricular hemorrhage [1].

5.4.3 Discussion of Late Preterm Mortality and Morbidity

5.4.3.1 Mortality Rates

Overall, death is a rare event among term and late preterm infants. There is some difference in overall survival rates in the neonatal period. The greatest disparity is apparent when comparing infants born at 34 weeks to infants born at term. The overall survival rate is 2.14% lower for infants born at 34 weeks, but is less than 1% at 35 and 36 weeks. By comparison, Kramer et al estimated perinatal mortality rates in Canada (excluding Ontario and rural Manitoba) and the United States. Two birth cohorts from Canada (excluding Ontario) for 1985-1987 (n=692 579), 1992-1994 (n=726 435) were used and two from the United States for 1985 (n=3 619 650) and 1995 (n=3 866 513). Infant mortality rates among all live births were 7.8 and 6.2 deaths per 1000 births in Canada and 10.4 and 7.5 deaths per 1000 births in the United States.

In assessing mortality rates, advances in neonatal care may help explain the similarity in survival rates across gestational ages and regions. Despite advances in mortality prevention, great disparities in morbidity rates are evident both in this study and in the literature.

5.4.3.2 Morbidity

Infections are a rare outcome among late preterm and term infants. Nevertheless, neonatal sepsis occurs 13.3 times more frequently in late preterm infants. High NICU admission frequencies among infants born at 34 weeks gestation may be due in part to hospital protocols which stipulate automatic NICU admission for infants with APGAR scores less than 7 at 5 minutes and birth weights less than 2250g. In large part it is hypothesized that differences in morbidity may be explained by developmental maturity disparities among term and late preterm infants. Considering late preterm infants comprise the largest and fastest growing proportion of preterm births, high morbidity rates among these infants may lead to sizable, but potentially preventable increases in health care spending.

5.4 Implications of morbidity differences among late preterm infants

5.4.1 Health Care Spending Implications Using US Costs as a Proxy

Although late preterm infants as a group are outnumbered by term infants by more than 15 to 1, late preterm infants have greater total length of stay in days in the NICU (Table 16 and 17). Using California NICU costs as a proxy, late preterm infants cost more per case at each gestational age than term infants (Table 18). Accordingly, Tables 19 and 20 demonstrate that although late preterm infants are far less numerous, they have incurred far greater NICU costs than term infants over the last 10 years at St Joseph's Health Care Centre in London Ontario. These results may be helpful for policy makers and health care providers who are projecting future health care costs. These results may provide support for efforts to delay premature delivery for non-medically indicated deliveries as both morbidity and health care costs could be reduced.

5.4.2 Estimating Cost Savings for Delaying Preterm Labor

The average neonatal hospital cost for an infant born at 34 weeks gestation is $7200. Delaying delivery by one week could potentially reduce costs by 42% to $4200. Similarly, delaying pregnancy to 36 weeks from 35 weeks, could decrease costs by 38%. To calculate potential savings arising from delaying labor, a method developed by Phibbs and Schmitt[124] can be used. Expected changes in costs are estimated by assuming that any infant born at 35 instead of 34 weeks gestation, would incur costs of an infant born at 35 weeks gestation. Since there is uncertainty in this assumption, 25^{th} and 75^{th} percentiles for costs are used to conduct sensitivity analyses. The lower end of the range of potential cost savings can be calculated as follows:

$S_L = 25^{th}$ percentile $Cost_I - 75^{th}$ percentile $Cost_S$

where $Cost_I$ is the cost distribution of the lower gestational ages that is the baseline, and $Cost_S$ is the cost distribution of the higher gestational age that the delivery was shifted to.

The upper value of the range of potential cost savings can be calculated by:

$S_U = 75^{th}$ percentile $Cost_I - 25^{th}$ percentile $Cost_S$

The same method can be used to estimate reductions in lengths of stay. Using Table 4 and 20, the estimated cost savings of delaying non-medically indicated preterm births at 34 weeks can be estimated as follows:

Savings from delaying birth at 34 weeks to 35 weeks= ($4528x240)= $1 086 720
Savings from delaying birth at 34 to 36 weeks =($7090x240)= $1 701 600
Savings from avoiding birth at 34 to 37 weeks =($8508x240)= $2 041 920

Thus, for illustrative purposes, delaying all preterm births at 34 weeks from one to three weeks could lead to savings of $1.1 million to $2.0 million at St Joseph's. Considering a CIHI study examining costs at 27 NICUs in Canada, savings from these units alone could range from $30 million to $54 million. Importantly, delaying premature birth will likely reduce costs for infants who were likely to survive despite being born preterm. However, delaying labor for those infants who were likely to die in the first few days will likely result in longer neonatal stays, and potentially greater NICU spending. However, shortening the stays of likely survivors is expected to occur more frequently resulting in greater savings than the costs arising from rare, averted deaths.

These results are important as promising therapies such as 17 alpha-hydroxyprogesterone caproate have been observed to be successful in delaying pregnancies in mothers who previously delivered preterm.[130] Furthermore, a recent cost savings analysis of 17 alpha-hydroxyprogesterone caproate, estimated that initial neonatal hospital costs could be reduced by $3800/infant, life time medical costs could be reduced by $15 900 per infant and universal treatment of expectant mothers with a history of preterm labour could lead to discounted lifetime medical cost

reductions of greater than $2 billion annually.[10] Realistically it is not likely that all preterm births will be prevented by therapies such as 17 alpha-hydroxyprogesterone caproate.

5.5 Methodological Strengths

In addition to a stringent review and application of the relatively technical predictive modeling literature, this study is strong due to the quality and comprehensive nature of the data. Accordingly, the results should be highly internally valid and therefore immediately useful for neonatologists managing late preterm infants at St Joseph's Health Care London. Throughout the modeling process a consistent focus on developing a clinically useful tool was maintained. The grouping and dichomotomizing of multi-level variables makes this tool not only easy to use, but widely applicable. As well, this study is both strong and unique in that it is rare to see maternal and neonatal characteristics assessed in combination as many studies only have an NICU database available and lack the important obstetric perspective. Most importantly, this model is unique in its ability to take into account all relevant risk factors in order provide each individual infant with an estimate of risk.

5.6 Methodological Limitations

A number of limitations are apparent in considering this study. This study was only conducted at a single center, which likely limits generalizability. By dichotomizing variables, information is lost at the expense of simplicity and clinical functionality. Similarly, certain variables were undoubtedly reported better than others. Considering maternal alcohol use for example, one study by St Joseph's neonatologists indicated that women often failed to honestly or accurately report alcohol consumption. Up to 10 fold differences were observed between reported and observed alcohol metabolites measured in the baby's meconium (Personal Communication). Variables like maternal smoking and drug use present similar issues. At the least, dichomtomizing lumps those who admitted to smoking, drinking or using drugs together. However, the unexposed group may be contaminated by those who failed to admit substance

use. The inclusion of poorly measured or heterogenous variables including alcohol, drug and tobacco use may also introduce noise into the multivariable modeling process. Models with and without these variables indicated very little difference in predictive ability and these variables were included in most models simply to add small, but non-zero predictive ability.

The present study is limited also in that the focus was on late preterm infants and term infants, and future studies may broaden this scope to include infants born before 34 weeks' gestation. Likewise, this study is limited to assessing risk of respiratory disorders, and ideally future models will incorporate all gestational weeks for the purposes of developing an index for all morbidities. Chart review on 34, 714 infants was not feasible and thus the accuracy of the data is limited by a lack of cross-referencing. Nevertheless, quality control measures are in place to maximize accurate input of the data. Ultimately, administrative databases depend on the accuracy of the data in the database.

The inclusion of all deliveries from all areas may potentially introduce referral bias. This may represent a limitation in that internal validity may be threatened which in turn may threaten external validity and generalizability to the general population. The specific goal throughout this study however, was to be clinically applicable and clinically relevant. Including all infants from all areas more accurately mirrors clinical practice for a neonatologist who must treat each infant that presents at his or her Level III Perinatal Center, regardless of where the mother resides geographically. Thus, the results of this study are likely highly applicable and generalizable to any Level III Perinatal Center in Canada where universal health care coverage offsets any costs such as NICU admission that a patient in other countries may be responsible for. Therefore due to disparities in health care insurance coverage in the United States for example, the results from this study are not likely generalizable to the general American population.

Data was unavailable for infants who were not admitted to the NICU, and there was no data on infants who were later re-admitted to the hospital after NICU discharge. It is assumed with great certainty that an infant who was not admitted to the NICU between birth and discharge did not develop RDS during this period. These results are assumed to be accurate between birth and discharge from the NICU. Other limitations associated with the measurement of outcome variables relates to the timing of their measurement. As outcomes are measured at birth or shortly thereafter, information in the database may contain a somewhat limited snap shot that may be subject to regression to the mean.

There may be problems associated with omitted variables. Although previous studies reported birth asphyxia as predictive of respiratory distress syndrome, we did not include birth asphyxia as a composite variable. Only about 0.25% of all term and late preterm infants met the SOGC criteria for birth asphyxia including APGAR at 5 minutes <7, arterial base excess >16 and arterial pH <7.00. Instead of a composite variable for birth asphyxia, these variables were included individually. The omission of protective or harmful risk factors may bias the results and may be due in part to publication bias. Similarly, some bias is certainly possible in the variable selection process, as only the author and one experienced neonatologist decided on all potential candidate variables. Potentially, numerous neonatologists could be consulted when developing the morbidity index for all gestational ages.

Like other studies making use of administrative databases, this study was unable to assess important covariates including severity and extent of neonatal morbidity, severity and management of maternal conditions, neonatal developmental issues, decisions related to the timing of delivery and reasons associated with preterm birth (ie obstetric intervention aimed at protecting life of mother, fetus and/or infant). Future studies which can incorporate this information may improve clinical decision making especially with respect to the ideal timing of delivery.

This study, also like other administrative database studies, may be limited by misclassification. Inconsistent reporting of gestational age for example could potentially bias the study findings. Overestimating the number of preterm births or misclassifying late preterm infants as term infants may lead to estimates that are biased towards the null. However, due to the observed strong associations which are far from the null, misclassification does not appear to have substantially altered the study findings.

Previous medical chart validation studies have reported inconsistencies and inaccuracies related to chronic hypertension and pregnancy induced hypertension records. Thus, this study and other administrative database studies may be limited by an inability to distinguish chronic from pregnancy related conditions. Resolution of this problem is complicated by the fact that women may not access health care until they are pregnant and thus chronic conditions may go undiagnosed. Ideally, this study would distinguish chronic and pregnancy related disorders, however this may not be realistic with administrative data and thus represents a limitation of the study findings.

Although quality control measures are in place, human error was expected. Any missing data however was expected to be missing completely at random. In comparing the frequency of respiratory disorders from the total sample to those with missing data, a small difference is evident (2.01% vs. 1.98%), however it is assumed that this will not drastically influence the results. It may be advisable to impute missing values as deleting cases with missing information on predictors can lead to bias and greater variance. Choosing not to impute or estimate missing values may represent a limitation of the study. However, the highest missing rate for one variable is 4%, with 5% missing overall. Harrell[73] states that a complete case analysis may be conducted when missing data on one variable is $\leq$5%. Considering 5% is missing as a whole, it may be reasonable to assume that conducting a complete case analysis will not distort the results considerably.

The decision to deliver an infant preterm must carefully weigh the risks of neonatal and maternal morbidity. Studies such as this one, and further studies may provide a better understanding of the risks associated with maternal conditions, late preterm birth and neonatal characteristics and thus may assist clinicians in anticipating possible complications, ordering tests, managing morbidity and planning staffing, beds and health care spending. Based on the results of this study and other previous studies, treating late preterm infants as term infants is not an evidenced-based approach.[15] More rigorous monitoring of late preterm infants is crucial in identifying, treating and limiting morbidity among late preterm infants. Furthermore, monitoring, preventing and treating maternal conditions, along with consideration of emerging therapies aimed at delaying delivery, will be crucial in both preventing late preterm birth and preventing newborn morbidity.

5.7 Future Research

Future research should focus on a number of important areas. Currently our understanding of long term outcomes among late preterm infants is limited. Future studies on long term outcomes will be important in providing earlier educational interventions and projecting potential educational spending associated with rising numbers of late preterm infants. Future research should also focus on generating predictive models for all ages and morbidities in order to better anticipate, treat and monitor preterm infants as a group. Finally, studies should aim to prevent morbidity through emerging therapies such as progesterone which delay preterm birth. As well, future studies should pursue drug trials in which it is ensured that medication aimed at limiting chronic maternal conditions is safe for both the mother and fetus or newborn. Thus efforts to prevent preterm birth or maternal morbidity may be most effective in mitigating the public health implications of rising late preterm birth rates.

Table 16. Length of Stay (days) in the NICU for the study population at St Joseph's Health Care London born between January 1996 and December 2006 stratified by gestational age.

Weeks Gestation	Number of Infants	Minimum	Maximum	Mean	Median	Total Days
34	325 (1.10)	0	169	12.00	9.00	3432
35	517(1.75)	0	44	8.17	6.00	2115
36	985(3.33)	0	33	7.23	4.00	1562
≥37	27762(93.83)	0	71	4.14	3.00	6207

Table 17. Total length of stay in the NICU (days) comparing term to late preterm infants born at St Joseph's Health Care in London, Ontario.

Weeks Gestation	Number of Infants	Total Days in the NICU
Late Preterm (34 to 36 weeks)	7109 (6.18%)	7109
Term (≥37 weeks)	27 762 (93.83%)	6207

Table 18. Estimated Neonatal Intensive Care Unit Costs by Week of Gestation for Surviving Infants at St Joseph's Health Care in London Ontario using Markup Adjusted NICU costs from the State of California.

Gestational Weeks	n	NICU LOS (days)	NICU Cost $1000/case	Total Cost
34	325	3432	7200	24 710 400
35	517	2115	4200	8 883 000
36	985	1562	2600	4 061 200
≥37	27762	6207	1100	6 827 700

Table 19 . Total Neonatal costs comparing term to late preterm infants born at St Joseph's Health Care in London, Ontario using California costs adjusted for markup as a proxy.

Weeks Gestation	Number of Infants	Total Cost
Late Preterm (34 to 36 weeks)	7109 (6.18%)	$37 654 600
Term (≥37 weeks)	27 762 (93.83%)	$6 827 700

Table 20. Estimated reductions in neonatal costs associated with 1 week increases in gestational age mean and range in USD adjusted for markup(modified from Phibbs and Schmitt [40])

Gestational Weeks	Delayed to 35 weeks	Delayed to 36 weeks	Delayed to 37 weeks
34 weeks (mean)	$4528	$7090	$8508
34 weeks (range)	(-$3926, $12 432)	(-$733,$12 474)	(-$389, $12508)

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Appendix

Results of Multiple Logistic Regression Analysis

Table A1. Results for Model 1 obtained using multivariable logistic regression.

Characteristic	Comparison	Odds Ratio (95% CI)	p value
Gestational Weeks	All weeks vs 39	0.521 (0.448 to 0.561)	**<0.0001**
PROM	Present vs Absent	0.992 (0.670 to 1.469)	0.970
Birth weight	Continuous	1.00 (1.00 to 1.00)	0.470
Maternal Age	Continuous	0.983 (0.967 to 1.00)	0.050
Labour	Absent vs Present	1.284 (0.912 to 1.087)	0.151
Chronic Hypertension	Present vs Absent	0.778 (0.939 to 1.540)	0.471
PIH	Present vs Absent	1.024 (0.905 to 1.158)	0.710
Bleeding	Present vs Absent	0.848 (0.637 to 1.130)	0.260
Diabetes	Present vs Absent	0.994 (0.930 to 1.061)	0.849
Delivery Mode	Cesearean vs Vaginal	1.553 (1.210 to 1.994)	**0.0005**
Smoking	Present vs Absent	1.199 (0.901 to 1.595)	0.213
Meconium	Present vs Absent	1.282 (0.955 to 1.722)	0.100
Chorioamnionitis	Present vs Absent	2.236 (1.305 to 3.830)	**0.0034**
Oligohydramnios	Present vs Absent	1.271 (0.797 to 2.028)	0314
Polyhydramnios	Present vs Absent	0.914 (0.452 to 1.846)	0802
Intrapartum Fever	Present vs Absent	2.237 (1.456 to 3.437)	**0.0002**
Alcohol use	Present vs Absent	1.375 (0.554 to 3.410)	0.492
Illicit Drugs	Present vs Absent	0.537 (0.259 to 1.116)	0100
Apgar at 1 minute	Continuous	0.841 (0.798 to 0.886)	**<0.0001**
Apgar at 5 minutes	Continuous	0.706 (0.639 to 0.780)	**<0.0001**
Arterial pH	Continuous	1.898 (0.303 to 11.876)	0.493
Arterial base excess	Continuous	0.955 (0.916 to 0.995)	**0.027**
Sex	Male vs Female	1.620 (1.335 to 1.964)	**<0.0001**

Table A2. Results for Model 2 obtained using multivariable logistic regression.

Characteristic	**Comparison**	**Odds Ratio (95% CI)**	**p value**
Gestational Weeks	All weeks vs 39	0.525 (0.488 to 0.565)	**<0.0001**
PROM	Present vs Absent	1.00 (0.675 to 1.482)	0.9993
Birth weight	Continuous	1.00 (1.00 to 1.00)	0.3922
Maternal Age	Continuous	0.985 (0.968 to 1.001)	0.0671
Labour	Absent vs Present	0.796 (0.566 to 1.118)	0.1879
HDP	Present vs Absent	1.104 (0.864 to 1.411)	0.4266
Bleeding	Present vs Absent	0.848 (0.637 to 1.129)	0.2599
Diabetes	Present vs Absent	0.666 (0.456 to 0.971)	**0.0347**
Delivery Mode	Cesearean vs Vaginal	1.591 (1.242 to 2.038)	**0.0002**
Smoking	Present vs Absent	1.189 (0.894 to 1.582)	0.2341
Meconium	Present vs Absent	1.220 (0.908 to 1.638)	0.1872
Chorioamnionitis	Present vs Absent	2.359 (1.387 to 4.013)	**0.0015**
Oligohydramnios	Present vs Absent	1.266 (0.798 to 2.019)	0.3229
Polyhydramnios	Present vs Absent	0.958 (0.474 to 1.938)	0.9049
Intrapartum Fever	Present vs Absent	2.234 (1.461 to 3.414)	**0.0002**
Alcohol use	Present vs Absent	1.315 (0.529 to 3.270)	0.5522
Illicit Drugs	Present vs Absent	0.618 (0.308 to 1.239)	0.1750
Apgar at 1 minute	Continuous	0.836 (0.794 to 0.880)	**<0.0001**
Apgar at 2 minutes	Continuous	0.706 (0.639 to 0.779)	**<0.0001**
Arterial pH	Continuous	1.76 (0.322 to 12.123)	0.4620
Arterial base excess	Continuous	0.953 (0.915 to 0.993)	**0.0220**
Sex	Male vs Female	1.590 (1.313 to 1.927)	**<0.0001**

Table A3. Results for Model 3 obtained using multivariable logistic regression.

Characteristic	**Comparison**	**Odds Ratio (95% CI)**	**p-value**
34 weeks gestation	vs 39	62.406 (38.662 to 100.733)	**<0.0001**
35 weeks gestation	vs 39	20.999(13.387 to 32.940)	**<0.0001**
36 weeks gestation	vs 39	11.573(7.715 to 17.362)	**<0.0001**
37 weeks gestation	vs 39	4.472(3.251 to 6.918)	0.3736
38 weeks gestation	vs 39	1.644 (1.128 to 2.397)	**<0.0001**
40 weeks gestation	vs 39	1.038(0.722 to1.491)	**<0.0001**
41 weeks gestation	vs 39	0.884(0.573 to 1.365)	**<0.0001**
PROM	Present vs Absent	0.882 (0.591 to 1.316)	0.5140
Birthweight	Continuous	1.000(1.00 to 1.001)	0.0562
Maternal Age	Continuous	0.985(0.968 to 1.002)	0.0774
Labour	Absent vs Present	1.521(1.066 to 2.170)	**0.0208**
HDP	Present vs Absent	1.134(0.882 to 1.458)	0.3257
Bleeding	Present vs Absent	0.713(0.376 to 1.350)	0.2986
Diabetes	Present vs Absent	0.758(0.503 to 1.144)	0.1870
Delivery Mode	Cesearean vs Vaginal	1.519(1.181 to 1.955)	**0.0012**
Meconium	Present vs Absent	1.140(0.844 to 1.539)	0.3927
Chorioamnionitis	Present vs Absent	2.110(1.224 to 3.640)	**0.0072**
Oligohydramnios	Present vs Absent	1.273(0.793 to 2.044)	0.3179
Polyhydramnios	Present vs Absent	0.977(0.480 to 1.988)	0.9490
Intrapartum Fever	Present vs Absent	2.054(1.336 to 3.157)	**0.0010**
Alcohol	Present vs Absent	1.442(0.571 to 3.644)	0.4390
Drugs	Present vs Absent	0.527(0.251 to 1.108)	0.0911
Smoking	Present vs Absent	1.234(0.924 to	0.1536

		1.648)	
Apgar at 1 minute	Continuous	0.850(0.806 to 0.897)	**<0.0001**
Apgar at 5 minutes	Continuous	0.711(0.642 to 0.787)	**<0.0001**
Arterial pH	Continuous	1.839(0.287 to 11.789)	0.525
Arterial base excess	Continuous	0.954(0.915 to 0.995)	**0.0275**
Gender	Male vs Female	1.586(1.305 to 1.927)	**<0.0001**

Table A4. Results for Model 4 obtained using multivariable logistic regression.

Characteristic	**Comparison**	**Odds Ratio (95% CI)**	**p-value**
34 weeks gestation	vs 37	22.186 (14.965 to 32.891)	**<0.0001**
35 weeks gestation	vs 37	8.467 (14.965 to 32.891)	**<0.0001**
36 weeks gestation	vs 37	5.656 (3.985 to 7.770)	**<0.0001**
Birthweight quintile 1	vs Birthweight quintile 3	1.520 (1.106 to 2.090)	**0.0018**
Birthweight quintile 2	vs Birthweight quintile 3	0.825 (0.597 to 1.138)	0.0748
Birthweight quintile 4	vs Birthweight quintile 3	0.877 (0.620 to 1.241)	0.2562
Birthweight quintile 5	vs Birthweight quintile 3	1.048 (0.723 to 1.517)	0.9034
Maternal age (<20 years)	vs Maternal age (20-34)	1.144 (0.740 to 1.768)	0.4983
Maternal age (>36 years)	vs Maternal age (20-34)	0.965 (0.762 to 1.224)	0.5113
PROM	Present vs Absent	0.881 (0.588 to 1.319)	0.5383
Labour	Absent vs Present	1.584 (1.119 to 2.242)	**0.0095**
HDP	Present vs Absent	1.193 (0.927 to 1.534)	0.1700
Bleeding	Present vs Absent	0.899 (0.671 to 1.204)	0.4744
Diabetes	Present vs Absent	0.881 (0.586 to 1.325)	0.5432
Delivery Mode	Cesearean vs Vaginal	1.471 (1.144 to 1.891)	**0.0026**
Meconium	Present vs Absent	0.962 (0.718 to 1.289)	0.7953
Chorioamnionitis	Present vs Absent	2.161 (1.258 to 3.713)	**0.0052**
Oligohydramnios	Present vs Absent	1.234 (0.769 to 1.980)	0.3845
Polyhydramnios	Present vs Absent	1.239 (0.614 to 2.499)	0.5500
Intrapartum Fever	Present vs Absent	1.865 (1.219 to 2.854)	**0.0041**
Alcohol	Present vs Absent	1.505 (0.593 to 3.823)	0.3896
Drugs	Present vs Absent	0.556 (0.263 to	0.1255

		1.178)	
Smoking	Present vs Absent	1.227 (0.919 to 1.638)	0.1654
Apgar at 1 minute	Continuous	0.852 (0.808 to 0.898)	**<0.0001**
Apgar at 5 minutes	Continuous	0.700 (0.632 to 0.774)	**<0.0001**
Arterial pH	Continuous	2.427(0.386 to 15.277)	0.3448
Arterial base excess	Continuous	0.956 (0917 to 0.997)	**0.0360**
Gender	Male vs Female	1.654 (1.362 to 2.010)	**<0.0001**

Table A5. Results for Model 7, the "Full Model".

	Original Index	Training	Test	Optimism	Corrected Index	N
Dxy	0.7422	0.7490	0.7258	0.0232	0.7190	1000
Intercept	0.0000	0.0000	-0.1202	-.1202	-.1202	1000
Slope	1.0000	1.0000	0.9601	0.0399	0.9601	1000