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Healthcare Outcomes and Resource Utilization Associated with Neonatal Hypoglycemia: Analysis of Data from the HCUP Kid's Inpatient Database

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HEALTHCARE OUTCOMES AND RESOURCE UTILIZATION ASSOCIATED WITH NEONATAL HYPOGLYCEMIA: ANALYSIS OF DATA FROM THE HCUP KID'S INPATIENT DATABASE

by

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ABSTRACT

HEALTHCARE OUTCOMES AND RESOURCE UTILIZATION ASSOCIATED WITH NEONATAL HYPOGLYCEMIA: ANALYSIS OF DATA FROM THE HCUP KID'S INPATIENT DATABASE

Brook T. Alemu
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Neonatal hypoglycemia is the most common metabolic abnormality in infants and is associated with neurological damage and death. The risk of developing hypoglycemia among infants born from diabetic mothers is even higher. Although much work has been performed addressing issues for treatment and care, research related to neonatal hypoglycemia has been focused on the clinical or individual level risk factors. Contextual risk factors such as hospital characteristics, neighborhood economic status, and regional variations were not considered in earlier studies. Additionally, although healthcare resources utilization of hypoglycemia has been adequately addressed in the adult population, this topic has not been studied in hypoglycemic neonates.

The overarching purpose of this dissertation was to investigate healthcare outcomes and resource utilization related to neonatal hypoglycemia. The first purpose was to conduct a systematic review in order to investigate whether previous studies only focused on clinical risk factors or included a broader health service-related contextual risk factors in assessing the determinants of neonatal hypoglycemia. The second purpose was to identify the key factors associated with increased hospital cost associated with neonatal hypoglycemia in the United States. The third and final purpose of the dissertation was to construct multi-level models that include individual-level and contextual-level characteristics.

The systematic review (Project I) determined that previous studies mainly focus on the clinical characteristics of infants and mothers. The systematic review suggested that contextual variables should be included in future research. Project II found that increased cost was observed, when more than five procedures were performed during the same hospitalization, when hospital bed size was between 100 and 300 or ≥ 400, when hospital length of stay exceeded 15 days, in teaching hospitals, in the presence of chronic conditions, comorbidities, prematurity, and death. In project III we found that infant of diabetic mothers had more than 5-fold increased risk of developing neonatal hypoglycemia compared to infants of non-diabetic mothers. Infants born in urban and teaching hospitals also had significantly higher chance of developing neonatal hypoglycemia. Project III also determined that the inclusion of the contextual risk factors improved the final model that was constructed to predict neonatal hypoglycemia.

To Sara A., Sisay M., and Bethlehem A.

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brother and mentor who provided comfort throughout the seemingly unbearable studying years. Betsy was also very supportive of my education. Her charm and wit made our office a fun place to work. Thank you both for your kindness, flexibility, and support.

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TABLE OF CONTENTS

Page

Chapter Page

LIST OF TABLES

LIST OF FIGURES

CHAPTER I

INTRODUCTION

Background

Health services research, among other things, examines determinants of health outcomes, healthcare cost, and quality of care usually at the population level and may investigate parts or the entire spectrum of care.[1,2] One important aspect is understanding the healthcare outcomes and efficient utilization of resources by including a broader spectrum of influencing factors. For neonatal hypoglycemia, although much work has been performed addressing issues for treatment and care[3] research in the area has been focused on the clinical determinants of the condition. Before discussing these issues in further detain, a synopsis of what neonatal hypoglycemia is and how it affects the newborn's health is warranted.

Neonatal hypoglycemia is the most frequently encountered metabolic disorder of newborn infants and has been linked to various adverse health outcomes.[4,5] Hypoglycemia is a metabolic abnormality in neonates due to inability to maintain glucose homeostasis.[6-8] Glucose is an essential primary substrate for the brain and its consumption by the brain is high and as a result, neurons and glial cells are susceptible to hypoglycemia.[9-15] Therefore, glucose homeostasis is crucial for the overall physical and neurological development of newborns.[6] Throughout gestation, maternal glucose provides all the glucose for the fetus via facilitated diffusion across the placenta according to a maternal-to-fetal glucose concentration gradient.[1,6] Hypoglycemia in neonates has been recognized as a cause of serious short-term and long-term morbidity for over 50 years.[16] Several clinical conditions could be associated with neonatal stress that could affect glucose homeostasis including infection, asphyxia, congenital heart disease, decreased substrate availability as a result of birth defects, prematurity and fetal growth

restriction, islet cell hyperplasia, erythroblastosis fetalis, and Beckwith-Wiedemann Syndrome.[4,17-21] In addition, endocrine abnormalities such as pan-hypopituitarism, hypothyroidism, adrenal insufficiency, increased glucose utilization, sepsis, and perinatal asphyxia could also be associated with neonatal hypoglycemia.[17,22] Although in most of these neonates, hypoglycemia is transient and asymptomatic, unrecognized hypoglycemia may lead to neonatal seizures, coma, and neurologic injury.[23,24] Prolonged neonatal hypoglycemia may also cause neuroglycopenic signs such as seizure, coma, cyanotic episodes, apnea, bradycardia or respiratory distress, and hypothermia.[4,22]

The risk of developing hypoglycemia among infants born from diabetic mothers is even higher.[25-32] Although the predisposing risk factors for the development of neonatal hypoglycemia in diabetic pregnancies are thought to be mainly related to poor maternal glycemic control, neonatal weight at birth, and gestational age at delivery[37,38], the full extent of the individual and contextual risk factors remains unclear. Previous studies of neonatal hypoglycemia[15,17-27,39-42] mainly focused on clinical risk factors such as poor maternal glycemic control, neonatal weight at birth, and gestational age at delivery as predisposing risk factors for neonatal hypoglycemia in diabetic pregnancies. However, contextual risk factors such as neighborhood socioeconomic status, hospital characteristics, and regional variations were not considered in these studies. Therefore, it is important to identify the various levels of risk factors that can predict neonatal hypoglycemia in this vulnerable population.

In addition to leading to serious acute[1,4] and chronic health problems[43], neonatal hypoglycemia also consumes a considerable amount of healthcare resources[4]. Although healthcare resource utilization of hypoglycemia has been adequately addressed in the adult population[44-49], this topic has not been studied in neonates with hypoglycemia. With the current

increase in the overall healthcare cost in the United States, there is a strong interest to enhance efficacy through reform and system improvement.[51,51] A better understanding of factors associated with healthcare resource utilization such as hospitalization cost and length of stay for neonates with hypoglycemia may help hospitals improve the efficiency of the care they provide while maintaining high quality of care.

Statement of the Problem

Estimates for neonatal hypoglycemia are between 3% and 29% of all pregnancies in the United States.[1,26] The risk of developing hypoglycemia among infants born from diabetic mothers is even higher.[25-32] Hypoglycemia occurs in approximately 8-30% of neonates born to mothers with diabetes[33,34], with an estimated incidence rate of approximately 27% among infants born to women with diabetes compared to 3% among apparently healthy full-term infants born to nondiabetic women.[12-13] Previous studies[15,17-27,39-42] mainly focused on clinical risk factors without considering the contextual risk factors for the development of neonatal hypoglycemia. In addition to leading to serious acute[4] and chronic health problems[43], neonatal hypoglycemia also consumes a considerable amount of healthcare resources.[52] With this overarching problem, this dissertation plans to address three problem areas that will be carried out with three interrelated but independent research projects.

Problem 1

Although the predisposing risk factors for the development of neonatal hypoglycemia in diabetic pregnancies are thought to be mainly related to poor maternal glycemic control, neonatal weight at birth and gestational age at delivery [37,38], the full extent of individual and contextual level determinants of neonatal hypoglycemia remain unclear. For health services research, it is important to investigate whether previous studies only focused on clinical risk factors or

included broader contextual risk factors in assessing the determinants of neonatal hypoglycemia. Conducting the systematic review on the topic will examine, collate, and synthesize the current collective evidence on the subject matter.

Problem 2

Although healthcare resource utilization of hypoglycemia has been adequately addressed in the adult population[44-49], this topic has not been studied in neonates with hypoglycemia. Therefore, identifying predictors of hospital cost estimates associated with neonatal hypoglycemia is important for efficient allocation of resources. Additionally, most cost estimate studies use total hospital charge as a proxy measurement for actual cost.[53] This may lead to drawing unwarranted conclusions about efficiency in hospital resource utilizations.[53] Therefore, using actual cost is important to accurately identify factors associated with increased hospital cost related to neonatal hypoglycemia.

In this regard, the Kids' Inpatient Database provides a separate cost-to-charge-ratio data file that will enable us to convert total hospital charge to total cost.[54] This will maximize the accuracy of the hospital cost estimation at the national level. Identifying the key factors associated with increased hospital cost is important to improve health outcomes and minimize hospitalization costs in these priority populations. To date, no study has been conducted to estimate hospitalization cost and identify predictors related to neonatal hypoglycemia.

Problem 3

Neonates with hypoglycemia are prone to different acute[37] and chronic health problems.[43] In the short run, newborns may experience jitteriness, hypotonia, lethargy, irritability, apnea, tachypnea, poor feeding, hypothermia, and seizures.[55] Later in their life, they may experience a neurodevelopmental delay or even death.[45,46] The risk of developing hypoglycemia among

infants born from diabetic mothers is even higher.[35,56] Research in this topic[15,17-27,39-42] mainly focused on clinical risk factors such as poor maternal glycemic control, neonatal weight at birth, and gestational age at delivery as predisposing risk factors for the development of neonatal hypoglycemia in diabetic pregnancies. However, contextual risk factors such as neighborhood socioeconomic status, institutional characteristics, and regional variations were not considered in these studies. Due to lack of adequate knowledge about the potential individual and contextual level risk factors, the prevention of neonatal hypoglycemia has been difficult.[57]As a health service researcher, one should consider the contextual risk factors that has not been included in previous neonatal hypoglycemia research. Therefore, using multilevel models that include individual (demographic and clinical characteristics of mothers and infants) level and contextual (neighborhood, institutional characteristics, and regions) level characteristics in order to predict neonatal hypoglycemia is warranted.

Purpose of the Study

The dissertation will address the three identified problems described above. Accordingly, the first objective was to conduct a systematic review in order to investigate whether previous studies only focused on clinical risk factors or included a broader health service-related contextual risk factors in assessing the determinants of neonatal hypoglycemia. The second objective was to estimate hospitalization cost and identify the key factors associated with increased hospital cost associated with neonatal hypoglycemia in the United States. The third and final objective of the dissertation was to construct multi-level models that include individual-level and contextual-level characteristics in order to predict neonatal hypoglycemia in diabetic and non-diabetic pregnancies.

The Social Ecological Model

This dissertation will apply the social ecological model which captures several layers of factors that include the infant's biology, his/her immediate family/community environment, and the societal landscape that affects his/her development.[58] Therefore, to understand the numerous risk factors for a particular disease that affects an infant, these layers of the larger contextual or distal factors has to be considered in addition to the immediate individual or proximal level factors. The social ecological model was originally developed by Urie Bronfenbrenner over the span of several years.[58-61] However, Kenneth McLeroy[59] and Daniel Stokols[60] have also made significant contributions to the development of the social ecological model by applying it to other health-related topics such as health behaviors and health promotion.

Although the social ecological model has not been applied to the identification of risk factors associated with neonatal hypoglycemia, it has been widely used in several public health and epidemiological research and practice. This includes reproductive health[65], health education, and promotion[66], environmental health[66], violence prevention[67], chronic diseases such as obesity[68] and diabetes.[69] As practiced in these studies, while keeping the major components of the model, necessary modifications will be made to fit the current topic.

The original social ecological model developed by Bronfenbrenner[58] has five major components that include microsystem, mesosystem, exosystem, macrosystem, and chronosystem. These constitute the ecological environment which is conceived as a set of nested structure, each inside the next.[58] According to the theory, microsystem indicates the immediate environment that proximal processes operate to produce and sustain the child's development.[58,59] In the dissertation, demographics, clinical, and laboratory measures are considered to be the immediate factors in the development of neonatal hypoglycemia (Figure I.1). Mesosystem

comprises the linkage and process taking place between two or more settings such as the relationship between a mother and her child.[58,61] For example, the mother's health directly affects the health of a newborn child. Hypoglycemic neonates born from diabetic mothers are at higher risk than those born from non-diabetic mothers mainly because of the poor health condition of the mother.[35,56] Exosystem comprises the linkages and processes taking place in two or more settings, at least one of which does not contain the developing person, but in which events occur that indirectly influence processes within the immediate setting in which the developing person lives.[58] The exosytem considered in this dissertation are neighborhood and hospital characteristics that may affect neonates with hypoglycemia. Macrosystem indicates policy and societal culture that ultimately affect the particular conditions and process occurring in the development of a child.[59-62] As indicated in Figure I.1, regional variations and neighborhood socio-economic status are considered to be the macrosystem. The chronosystem encompasses change or consistency over time not only in the characteristics of the child but also in the environment in which the child lives.[62] Since time is not considered in the dissertation, we will only be focusing on the first four factors of the ecological model.

In the case of neonatal hypoglycemia, because of the intertwined relationship between the health of the mother and the newborn, the microsystem and mesosystem are classified as individual level characteristics (Figure I.1). Similarly, as exosystem and macrosystem are interrelated, the two systems are classified as contextual level characteristics. Therefore, in our current analysis, the two levels of characteristics will be examined. By combining both the individual and contextual level characteristics, we propose to build multilevel models that can predict the probability of developing neonatal hypoglycemia in diabetic and non-diabetic

mothers. As indicated in Figure I.1, the overlapping elliptical circles in the model illustrate how factors at one level influence factors at another level.

The application of such conceptual framework will enhance the current research in neonatal hypoglycemia by providing a broader perspective of the risk factors that were previously limited to clinical or individual level risk factors. In addition, the application of multilevel models, through taking complex survey design into consideration, will promote the use of advanced statistical methodologies in other areas of health outcomes research in the pediatric population.

Significance of the Study

For neonates to have a normal brain, adequate supply of glucose during infancy is crucial.[70] Therefore, the lack of this essential substrate at the early stage of growth may lead to various acute[4] and long term[43] life-threatening medical conditions. Specific groups of newborn infants, including infants having prematurity, macrosomia, intrauterine growth restriction, maternal diabetes, and sepsis, are at increased risk for hypoglycemia.[14,35,36] Neonatal hypoglycemia is a highly preventable medical condition[71] and yet it poses a significant threat to the health of newborns. Due to lack of adequate knowledge about the potential individual and contextual level risk factors, the prevention of neonatal hypoglycemia has been difficult.[57] Considering these multilevel characteristics in assessing the predictors for neonatal hypoglycemia is necessary to understand the complex interaction among various individual and contextual level factors that determine neonatal hypoglycemia. In addition, since neonatal hypoglycemia is strongly associated with diabetic pregnancies[33,72,73], the identification of the risk factors will also have important implications on mothers' health through effective prevention measures that can reduce high-risk pregnancies. It is expected that the results of the current

research will guide the prevention and control of adverse health outcomes associated with hypoglycemia in these priority populations.

The use of a conceptual framework to identify predictors of neonatal hypoglycemia is also lacking in current research on the topic. Although the primary objective of the current dissertation is not to test a theory, the use of social ecological model[58,63,64] as a conceptual framework will help us understand the complex influencing factors associated with neonatal hypoglycemia. The social ecological model defines complex layers of factors that affect the development of a child. That is the interaction between factors in the child's biology, his/her immediate environment and the societal landscape affecting his/her development. Using a conceptual framework in health outcomes research is a vital tool to insure that all essential risk factors are considered.[74]

Identifying predictors of hospital cost associated with neonatal hypoglycemia is important for efficient utilization and allocation of healthcare resources. However, healthcare resource utilization of hypoglycemia has only been studied in adult populations.[26-34] Furthermore, most cost estimate studies have used total hospital charge as a proxy measurement for actual cost.[53] However, this may lead to drawing unwarranted conclusions about economic efficiency and hospital resource utilizations.[53] Project II of the dissertation seeks to determine the predictors of hospital cost estimates by using actual cost rather than using hospital charges as a proxy for cost. In this regard, the Kids' Inpatient Database provides a separate cost-to-charge-ratio data file that will enable us to convert total hospital charge to total cost[54]. This will maximize the accuracy of the cost estimation at the national level. Identifying the key factors associated with increased hospital cost is important to improve health outcomes and minimize hospitalization costs in these priority populations.

Overall, the results of this dissertation are expected to improve scientific knowledge through the identification of multiple levels of risk factors based on a conceptual framework and appropriate application of rigorous statistical methodologies. Additionally, we anticipate that the proposed work will improve prevention of neonatal hypoglycemia and promote efficient utilization of hospital resources. The studies included in this dissertation were conducted in compliance with the institutional review board.

Specific Aims and Hypotheses

Aim 1: To conduct a systematic review in order to investigate whether previous studies only focused on clinical risk factors or included a broader health service-related contextual risk factors in assessing the determinants neonatal hypoglycemia.

Hypotheses 1: In the literature, all studies will focus on the individual level characteristics as determining risk factors for neonatal hypoglycemia.

Aim 2: To determine the overall hospital cost estimates and identify predictors of increased hospital cost in neonates with hypoglycemia.

Hypotheses 2.1: Healthcare outcome measures including length of stay, comorbidities, mortality, prematurity, number of procedures, hospital bed size, chronic conditions, and hospital teaching status will predict increased hospital cost associated with neonatal hypoglycemia.

Hypotheses 2.2: Neonates with hypoglycemia will consume a higher percentage of resources associated with hospital births while accounting for a smaller percentage of hospitalization.

Aim 3: To construct multilevel models for individual and contextual predictors of neonatal hypoglycemia among diabetic and non-diabetic pregnancies.

Hypotheses 3.1: Infants born from diabetic mothers have significantly higher chance of developing hypoglycemia compared to those born from non-diabetic mothers.

Hypotheses 3.2: The addition of the contextual risk factors will enhance the predictive power of the model that will be constructed to predict neonatal hypoglycemia in diabetic and non-diabetic pregnancies.

Operational Definitions

Comorbidities: ICD-9-CM codes indicating any of the following medical conditions; jitteriness (796.9), hypotonia (781.3), lethargy (799.22), apnea (786.03), tachypnea (786.06), poor feeding (783.3), hypothermia (991.6), sepsis (995.91& 771.81), seizures (345.x), and neurodevelopmental disorder (315.x). [75, 76]

Contextual-Level Characteristics: Contextual risk factors such as neighborhood socio-economic status, hospital characteristics, seasons, and regions.

Cost-to-Charge Ratios (CCRs): CCRs enables the conversion of actual cost from total hospital charge (i.e. Hospital Costs = Cost-to-Charge Ratios*Total Charges).[77, 78]

Diagnosis Related Groups, version 24 (DRG24): A statistical system of classifying any inpatient stay into one of originally 467 groups. DRG24 is assigned by the Centers for Medicare and Medicaid Services DRG grouper algorithm during HCUP processing and has been available since 2006.[54]

Exosystem: Comprises the linkages and processes taking place in two or more settings, at least one of which does not contain the developing person, but in which events occur that indirectly influence processes within the immediate setting in which the developing person lives.[58, 59]

Hospital File: It contains variance estimation data elements, linkage data elements, and data elements that describe hospital characteristics.[54]

Hypoglycemia: A metabolic abnormality in neonates due to inability to maintain glucose homeostasis.[1,2]

In-hospital Births: They are identified by any principal or secondary diagnosis code in the range of V3000 to V3901 with the last two digits "00" to "01" whereby the patient is not transferred from another acute care hospital or healthcare facility.[54]

Individual-level characteristics: Demographics, clinical, and laboratory measures of the mother and the child.

Kids' Inpatient Database (KID): KID is a database developed by the Healthcare Cost and Utilization Project (HCUP) of the Agency for Healthcare Research and Quality (AHRQ) which contains a sample of pediatric discharges from all community, non-rehabilitation hospitals in 44 participating States.[54]

Macrosystem: It indicates policy and societal culture that ultimately affect the particular conditions and process occurring in the development of a child.[58,59]

Major Diagnostic Categories (MDC): Obtained by classifying all possible principal diagnoses (from ICD-9-CM) into 25 mutually exclusive diagnosis areas.[54]

Maternal Diabetes: Diagnosis information (DX1-DX25) or Major Diagnosis Category (MDC) are coded as '250.00' to '250.93' and the variable neonatal/maternal flag (NEOMAT) indicates a maternal diagnosis (codes as '1' or '3').[75,76]

Mesosystem: Comprises the linkage and process taking place between two or more settings such as the relationship between a mother and her child.[58,59]

Microsystem: Indicates the immediate environment that proximal processes operate to produce and sustain a child's development.[58,59]

Neonatal hypoglycemia (NH): If any of the diagnosis information (DX1-DX25) variables is equal to '775.6', the newborn infant is identified as having experienced neonatal hypoglycemia during his or her hospital stay.[75,76]

The International Classification of Diseases, 9th version (ICD-9-CM): ICD-9-CM is the United States health system's adaptation of international ICD-9 standard list of six-character alphanumeric codes to describe diagnoses.[76]

Assumptions

The primary assumptions of this dissertation were the following:

For Chapter III and IV:

1. Kids' Inpatient Database developed by the Healthcare Cost and Utilization Project of the Agency for Healthcare Research and Quality is accurate and valid.
2. The definition of neonatal hypoglycemia is universally accepted by the medical community.
3. All symptomatic and asymptomatic neonatal hypoglycemia were included in the database.
4. The International Classification of Diseases, 9th version, is an accurate coding mechanism to identify diagnosis and procedures associated with neonatal hypoglycemia.
5. The social ecological model assumes that multiple factors influence health.[63,64]
6. There is a reciprocal relationship between individuals and their environments.[63,64]
7. Human-environment interactions can be described at varying levels of organization.[64]
8. All hospital participated in the Healthcare Cost and Utilization Project has proper data entry and management systems.

For Chapter IV:

1. Assumptions 1-8 for Chapter III and IV
2. Individual level and contextual level characteristics encompass all potential risk factors for the development of neonatal hypoglycemia.

Delimitations

1. Subjects are male and female neonates discharged from community, non-rehabilitation hospitals in the United States.
2. The study will be limited to uncomplicated and complicated in-hospital births and will not include all other pediatric cases.
3. The study will be limited to the 44 participating States in Healthcare Cost and Utilization Project.

Limitations

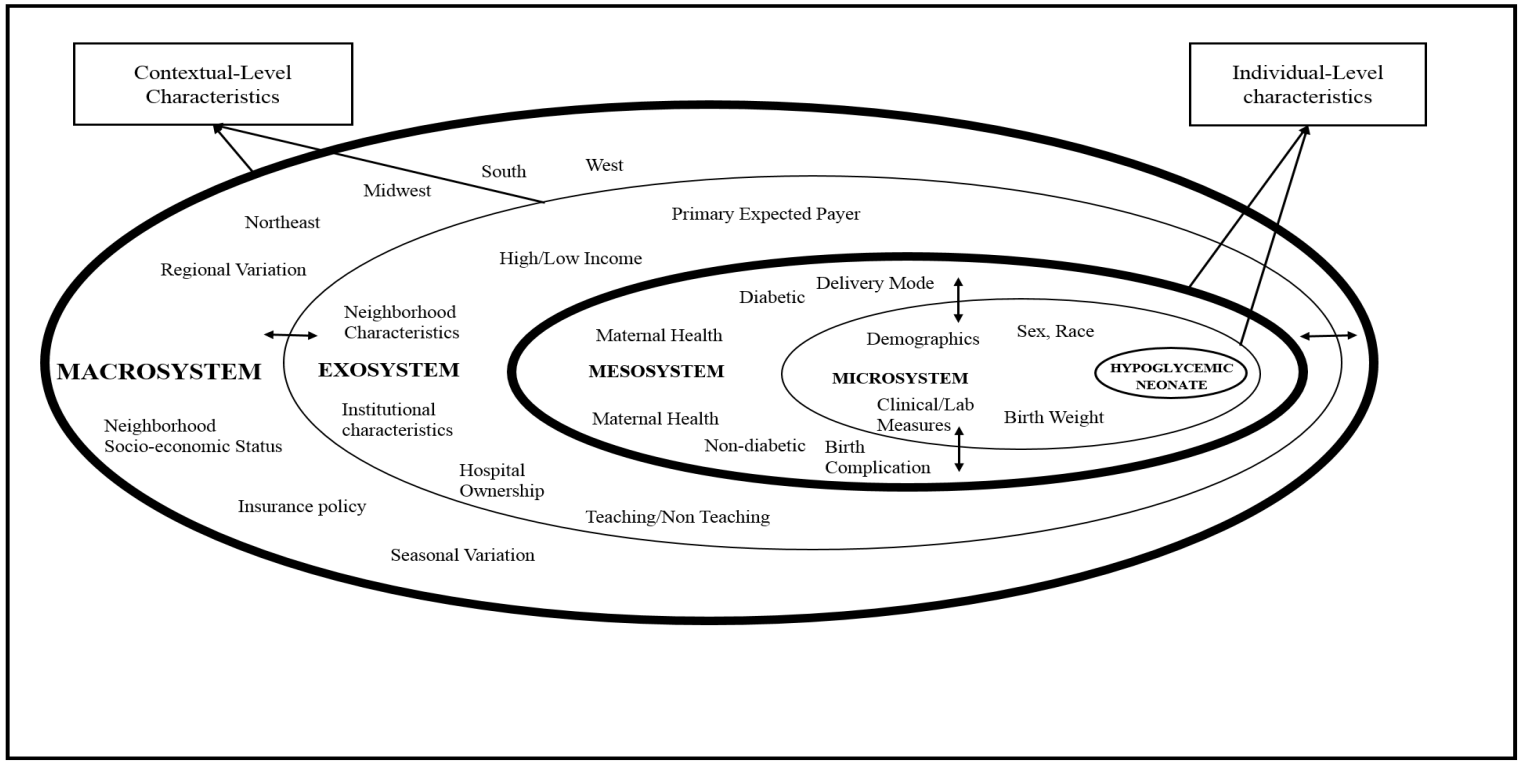
For Chapter III and IV:

1. Inconsistencies in the collection of data and quality problems may hinder the use of hospital discharge data for specific applications such as comparative analysis.[79,80]
2. Errors in providers' understanding of diagnostic coding/groupings (e.g., ICD-9-CM, DRG, MDC) may lead to misclassification.[81]
3. Co-morbidities (reported as secondary diagnosis codes) may be underreported, particularly for some conditions that are not directly associated with cause of admission.[82,83]
4. Only 44 states participate in the in Healthcare Cost and Utilization Project. Even in those states that mandate hospital participation, certain types of hospitals, such as Veterans'

Administration and Indian Health System facilities, are typically exempt. Incomplete data can hinder efforts to use discharge data at the State and national level.[81]

5. Submission of discharge data is voluntary in some states and submission of certain data elements may be voluntary even in states that mandate hospital participation resulting in missing data points (e.g. race and ethnicity).[81]

Figure I.1. Modified Ecological Model for Risks Associated with the Development of Neonatal Hypoglycemia



CHAPTER II

REVIEW OF THE LITERATURE

The purpose of this chapter is to systematically review the literature regarding whether previous studies only focused on clinical risk factors or included broader contextual risk factors in assessing the determinants of neonatal hypoglycemia. Chapter II (Project I), Neonatal hypoglycemia in diabetic mothers: a systematic review, critically appraises the literature to evaluate risk factors of neonatal hypoglycemia. PubMed and EBSCOhost search engines were used to identify published studies. A modified STROBE statement was also used to assess studies' strengths, weaknesses, and generalizability. Overall, this chapter provides a synthesis of the literature regarding the relationship between hypoglycemia and diabetic pregnancies. The overall evidence suggested that the studies included in the systematic review mainly focused on clinical risk factors. The reviewed risk factors were classified into two: infant-related and mother-related. Based on the gap observed in the literature, directions for future research were provided.

PROJECT I: NEONATAL HYPOGLYCEMIA IN DIABETIC MOTHERS: A SYSTEMATIC REVIEW

Introduction

Neonatal hypoglycemia is a common metabolic abnormality in newborns due to inability to maintain glucose homeostasis.[84,85] Glucose is an essential primary substrate for the brain and its consumption by the brain is high and as a result, neurons and glial cells are susceptible to hypoglycemia.[86,4] Therefore, glucose homeostasis is crucial for the overall physical and neurological development of newborns.[6] Throughout gestation, maternal glucose provides all the glucose for the fetus via facilitated diffusion across the placenta according to a maternal-to-fetal glucose concentration gradient.[6] Hypoglycemia was defined by studies as early as 1937 as "mild" (2.2–3.3 mmol/l), "moderate" (1.1–2.2 mmol/l), and "severe" (<1.1 mmol/l).[7] A specific blood glucose concentration to define neonatal hypoglycemia for infants is a subject of controversy.[8,11, 87] However, it is generally accepted that neonatal hypoglycemia is defined by a plasma glucose level of less than 30 mg/dl or 1.65 mmol/l in the first 24 hours of life.[12] To date, hypoglycemia remains one of the major metabolic abnormalities of the newborn.[13,15, 88]

The most common symptoms of neonatal hypoglycemia are shakiness, tachycardia, lethargy, and temperature irregularities.[23, 39] In the presence of these symptoms, neonatal hypoglycemia is defined as capillary plasma glucose of less than 46 mg/dl (2.6 mmol/l).[23] Prolonged neonatal hypoglycemia may also cause neuroglycopenic signs such as seizure, coma, cyanotic episodes, apnea, bradycardia or respiratory distress, and hypothermia.[4, 22]

Several clinical conditions could be associated with neonatal stress that could affect glucose homeostasis of the newborn infant including infection, asphyxia, congenital heart disease, decreased substrate availability as a result of birth defects, prematurity and fetal growth

restriction, islet cell hyperplasia, erythroblastosis fetalis, and Beckwith-Wiedemann Syndrome.[4,15, 17-21] In addition, endocrine abnormalities such as pan-hypopituitarism, hypothyroidism, adrenal insufficiency, increased glucose utilization, sepsis, and perinatal asphyxia could also be associated with neonatal hypoglycemia.[17,18] Although in most of these neonates, hypoglycemia is transient and asymptomatic, unrecognized hypoglycemia may lead to neonatal seizures, coma, and neurologic injury.[23, 41]

The risk of developing hypoglycemia among infants born from diabetic mothers is even higher.[25-35] Hypoglycemia occurs in approximately 8-30% of neonates born to mothers with diabetes[33,34], with an estimated incidence rate of approximately 27% among infants born to women with diabetes compared to 3% among apparently healthy full-term infants born to nondiabetic women.[35, 36] Although the predisposing risk factors for the development of neonatal hypoglycemia in diabetic pregnancies are thought to be mainly related to poor maternal glycemic control, neonatal weight at birth, and gestational age at delivery[37,38], the full extent of the individual and contextual risk factors remains unclear. In addition, to date, no systematic reviews of the available studies exist.

Our objective is to conduct a systematic review of the literature on the risk factors for hypoglycemia in infants of diabetic mothers. Accordingly, all relevant empirical studies on neonatal hypoglycemia in diabetic mothers were reviewed and appraised for methodological quality. The results were summarized in a way that informs both clinical practice and future research.

Method

Search Strategy

We identified published studies using PubMed and EBSCOhost search engines. The search was carried out by using the population, intervention, control, and outcome (PICO) strategy. The following concepts and related key words searched in their respective PICO category and they were finally combined together: (1) neonatal terms (‘neonate, ‘neonates’, ‘neonatal’, ‘newborn’, ‘newborns’, and ‘infant’), (2) diabetes and pregnancies terms (‘pregnancy in diabetics’, ‘diabetic mothers’, ‘diabetic pregnancy’, ‘pregnancy in diabetes’), and outcome terms (‘hypoglycemia’, ‘hypoglycaemia’, ‘hypoglycemic’, and ‘neonatal hypoglycemia’). We included all empirical studies published in the English language between January 1, 2000, and March 31, 2016. Additional studies were identified from reference lists of identified articles. The following inclusion and exclusion criteria were used to identify relevant articles:

Inclusion criteria: (1) observational studies, (2) neonatal hypoglycemia is used as the primary outcome of interest, (3) neonates born from type 1 (defined as blood glucose ≥11.1 mmol\l), type 2 (defined as fasting blood glucose ≥ 7.0 mmol\l or ≥11.1 mmol\l during OGTT) or gestational diabetic mothers (defined as having at least two plasma glucose measurements during the diagnostic test of the following OGTT glucose threshold values: 5.3 mmol/l fasting, 10.0 mmol/l at 1 hr, 8.7 mmol/l at 2 hr, and 7.8 mmol\l at 3 hr), (4) has appropriate comparison group, (5) neonatal hypoglycemia diagnosed within 3 days of life, and outcome defined in the ranges of 20 to 50 mg/dl or 1.1-2.8 mmol/l.

Exclusion Criteria: (1) animal studies, (2) review articles, (3) articles published in a non-English language, (4) articles published prior to 2000, and (5) poorly defined or no comparison group.

Data Abstraction and Overall Assessment of Studies

The abstracts of all potential publications were reviewed initially by the first (B.A.) and the second (O.O.) authors to identify eligible publications for further review. Full text screening was made by the two authors through a detailed review of the complete text of each articles using the inclusion/exclusion criteria as a guideline. The two authors then independently reviewed publications that were identified for inclusion. Relevant study attributes were extracted from the selected publications using standardized forms developed for the systematic review project by the authors. A third author (M.A) mediated to resolve any disagreements between the authors.

The STROBE (Strengthening the Reports of Observational Studies in Epidemiology) Statement (checklist of items that should be included in reports of observational studies) was used to assess studies' strengths, weaknesses, and generalizability. An explanation and elaboration article that discusses each checklist item and gives methodological background and published examples of transparent reporting were used in conjunction with the STROBE checklist.[41] As most of the studies on this topic are observational, we used the STROBE checklist as a guide to systematically evaluate the studies that were included in this review. The STROBE checklist has 21 items with 15 items relevant to all three study designs (i.e. cohort, case-control, and cross-sectional studies) and 4 are specific for each. However, items 1-3 (background and objectives), 6b (for matched studies), 11(quantitative variables), and 22 (funding information) were removed as they were not applicable to the included studies. Therefore, a modified 15-item STROBE checklist was used to critically appraise study quality for this systematic review.

Results

Study Selection

A total of 1233 titles were identified on PubMed and EBSCOhost in the initial literature search, 1202 of which were excluded by the first screening based on the title or abstract, leaving 31 articles for full-text review (Figure II.1). Thirteen of these studies met the inclusion criteria and an additional 3 articles were included from reference lists[25,33,34], resulting in 16 eligible studies, most of which were based on observational studies (Table II.1). The main reasons for excluding studies after full review were (i) hypoglycemia was not listed as primary outcome, (ii) comparison group were not defined and, (iii) hypoglycemia was not defined within the specified range of 1.7-2.8 mmol/l.

We identified four prospective cohorts, one nested case-control and ten retrospective cohort studies that examined the various clinical risk factors for hypoglycemia in diabetic mothers. Mother's diabetes types included gestational diabetes mellitus (GDM), type-1 diabetes mellitus (T1D), and type-2 diabetes mellitus (T2D). Other details on included studies are summarized in Table II.1. A total of 13,248 infants were identified in the 16 included studies. The key findings are described in the following section.

Critical Appraisal

The two authors agreed initially on 228 out of 240 (95%) items on the modified STROBE checklist. All disagreements were resolved by discussion among the two reviewers. Overall, the quality scores of the included studies ranged from 26.7% to 86.7%, with a median of 46.7%. Included studies were classified as high quality if the individual quality scores were ≥80%, studies were classified as moderate quality for quality scores between 79% and 60% and studies with quality scores below 59% were classified as low quality. Accordingly, a total of five high quality[15,39,26-28], two moderate quality[29,30], and nine low quality studies were identified.[12,21,31,32,33-38] The individual item, assessment responses, and quality scores can be found in Table II.3.

Clinical Significance and Risk Factors of Neonatal Hypoglycemia

Four prospective cohort studies[21,25,91,92] examined various risk factors of hypoglycemia in neonates of women with different diabetes type. Roux *et al.*[25] prospectively examined glucose levels in infants of women with GDM and the influence of maternal, gestational and peripartum factors on the development of hypoglycemia. They found that hypoglycemic infants were more frequently large for gestational age (LGA) (29.3% vs 11.3%), had lower umbilical cord pH (7.28 vs 7.31), and their mothers had more frequently been hyperglycemic during labor (18.8% vs 8.5%). The study obtained data from infants born in a hospital to mothers with GDM over a period of 30 months. After adjusting for confounding factors, umbilical cord venous pH [odds ratio (OR) 0.04, 95% Confidence Interval (CI) 0.261–0.99)] and Pakistani origin patients (OR 2.94, 95% CI 1.14 7.55) were significantly and independently associated with hypoglycemia. Similarly, Agrawal *et al*.[21] found that infants of mothers diagnosed with GDM or preexisting diabetes prior to 28 weeks gestation were at a higher risk of developing hypoglycemia compared to those with maternal diabetes diagnosed at 28 weeks gestation (OR 7.2, 95% CI 1.3-40.7). However, there was no difference in the cord blood glucose levels between infants with or without hypoglycemia.

Sarkar *et al.*[91], on the other hand, examined the risk of developing hypoglycemia in infants born to women with diet-controlled GDM (GDM-A1), insulin-requiring (GDM-A2) and insulin-dependent diabetes (IDDM) at ≥ 36 weeks of gestation compared to infants born to healthy controls using data obtained over a period of 16 months. They found that there is no significant difference in the incidence of hypoglycemia in infants born to GDM-A1 (4.3%) compared to infants born to healthy controls (4.4%). They concluded that infants born to GDM Class A1 women at ≥ 36 weeks of gestation are not at increased risk of developing

hypoglycemia. On the other hand, Cordero and Landon[35,36] found a 3% incidence of transient hypoglycemia in healthy full-term infants born to nondiabetic women.

Using national data from the Swedish Medical Birth Registry, Persson *et al.*[92], investigated whether disproportionate body composition is a risk factor for perinatal complications, including hypoglycemia, in LGA infants born to mothers with T1D. Their findings showed that there was no significant difference in the risk for hypoglycemia between proportionate LGA (OR 1.42, 95% CI 1.01-2.0) and disproportionate LGA infants (OR 1.42, 95% CI 0.97-2.08) compared to appropriate for gestational age (AGA). Disproportionate LGA was defined as Ponderal Index (PI) >90th centile and proportionate <90th centile LGA according to gestational age and sex. Similar results were obtained by Leperque *et al*.[93] while Ballard *et al.*[94] and Bollepalli *et al*.[95] contrasted the result. Furthermore, Ferrara *et al.*[96] found that women with GDM defined by American Diabetes Association (ADA) criteria had an increased risk of having an infant with hypoglycemia (OR 2.61, 95% CI 0.99–6.92), although not statistically significant. The study used a group practice database that included 16 hospitals and provides medical services to approximately 3.0 million people. Their findings supported the ADA 2000 recommendations (GDM, 2000) to adopt a lower plasma glucose thresholds proposed by Carpenter and Coustan[97] for the diagnosis of GDM.

We also identified ten retrospective cohort studies and one nested case-control study[23,33,34,72,70,95,98-101] that examined the risk of developing hypoglycemia in infants born to mothers with different diabetic conditions. Most of these observational studies were conducted using single institution databases.

Garcia-Patterson *et al.*[72] examined the relationship between maternal pre-pregnancy BMI and hypoglycemia among infants born to women with GDM with a gestational age higher than

22 weeks using databases from a tertiary care center. Maternal pre-pregnancy BMI ≥25 kg/m^2 was determined as an independent predictor of hypoglycemia irrespective of potential intermediate variables being included in the model (OR 2.11, 95% CI 1.10–4.03) or without (OR 2.66, 95% CI 1.44–4.92). The rate of hypoglycemia in neonates was 3% (63). On the other hand, Maayan-Metzger *et al.*[33] examined the impact of duration of delivery room breastfeeding on blood glucose levels (BGL) during the first hours of life among term neonates born to mothers with GDM and to examine its relationship with hypoglycemia using a medical center database. Among the neonates in the study group, 29 (36.7%) had at least one hypoglycemia value of <47 mg/dl, and 8 (10.1%) had a value of <40 mg/dl in the first 8 hours of life. After controlling confounding factors such as birth weight, delivery number, and grasp evaluation, only lower cord blood glucose significantly predicted hypoglycemia for each decrease of 10 mg/dl (OR 2.11, 95% CI 1.1–4.03). The mean glucose at the first hour of life was 56.2 mg/dl (range 28–105 mg/dl). A trend towards a higher incidence of normoglycaemia (>40 mg/dl) was recorded for the longer duration of delivery room breastfeeding subgroup (OR 1.923, 95% CI 0.984-3.76). However, the duration of delivery room breastfeeding did not influence the rate of hypoglycemia. In contrast to this findings, Chertok *et al.*[102] found that breastfed infants had a significantly higher mean BGL (3.20 mmol/l) compared to those who were formula fed (2.68 mmol/l). One reason for the different results could arise from the definition of hypoglycemia. In Garcia-Patterson, *et al.*[72] hypoglycemia was defined as “normal” (≥2.6 mmol/l), “mild hypoglycemia” (2.2–2.5 mmol/l), “moderate hypoglycemia” (1.7–2.1 mmol/l) and “severe hypoglycemia” (1.7 mmol/l). While Chertok *et al.*[102] defined hypoglycemia as BGL < 1.93 mmol/l and borderline hypoglycemia were 1.93–2.48 mmol/l. In addition to differences in

measurement, the difference in adjusting factors may have contributed to the apparent contrast in the results.

Ramos *et al*.[23] assessed factors associated with hypoglycemia in a cohort of pregnancies with T2D and GDM. The incidence of hypoglycemia in this study was 18% (44/242). The frequency of hypoglycemia between the glyburide and insulin-treated pregnancies did not differ significantly (23% vs. 27%). Maternal age ≥35 years (OR 2.78, 95% CI 1.13–6.85) and Ponderal Index (OR 5.59, 95% CI 1.34–23.25), a measure of fetal adiposity, significantly predicted hypoglycemia. Similarly, Majeed *et al.*[73] investigated if maternal glycated hemoglobin (HbA1c) was a good predictor of hypoglycemia. As hypothesized HbA1c in late pregnancy, between 36 and 38 weeks of gestation, significantly predicted hypoglycemia in the newborn, giving an area under the ROC curve of 0.99 with a 95% CI of 0.992 to 1. A ROC curve determined the optimal cut-off point for maternal HbA1c level in predicting hypoglycemia, was 51 mmol/l (6.8 %). However, various studies gave mixed results regarding the association between maternal HbA1c and hypoglycemia. Using logistic regression Kline & Edwards 2007 also found that a third trimester HbA1c of > 6.5% (47.54mmol/l) had a stronger association with neonatal hypoglycemia requiring intervention when compared to maternal delivery BGLs (OR 3.89, 95% CI 1.42-10.68). However, Taylor, *et al.*[100] found that hypoglycemia correlates with maternal hyperglycemia in labor, not with HbA1c during pregnancy. They found that maternal blood glucose during labor influenced neonatal blood glucose if over 8 mmol/l.

Discussion

Neonatal hypoglycemia is the most common metabolic abnormality in newborn infants due to the inability to maintain glucose homeostasis[13,84] To date, the full extent of various risk factors of hypoglycemia in infants of diabetic mothers are not known. Our findings are the result

of a systematic search for all relevant studies on hypoglycemia in diabetic mothers and critical appraisal of methodologies and study quality assessment.

We found few prospective studies that carefully examined the clinical and demographic risk factors of hypoglycemia among neonates. However, the majority of studies identified in our literature review were observational retrospective design that used existing institutional databases. As a result, after assessing studies' strengths, weaknesses, and generalizability using the STROBE Statement[103], the overall quality of evidence was low. The clinical risk factors in these studies can be broadly classified into two: infant-related and mother-related clinical risk factors. The infant-related significant risk factors identified in these study were SGA, LGA[43,70,95], macrosomia, prematurity[94], lower cord blood glucose[33], Ponderal Index[23], and male sex[101]. On the other hand, mother-related significant risk factor of hypoglycemia includes maternal hyperglycemia, ethnic origin[25], diabetes diagnosed prior to 28 weeks of gestation[21], pre-pregnancy BMI ≥25 kg/m2[72], hyperglycemia, blood glucos[100], maternal diabetes type[94], and material HbA1c.[73] Although several other risk factors were considered in these studies, the statistically significant risk factors are important for understanding the clinical management of the study population and future studies using multilevel design of risk assessment. Irrespective of diabetes type, it appears that infants of diabetic mothers have a higher risk of hypoglycemia compared to those born to normal mothers.[91, 96]

Overall, the results of the individual studies assessed various risk factors. However, a consistent pattern of risks of hypoglycemia among infants of diabetic mothers was not identified which may be the result of several factors. First, as the definition of clinical significance of hypoglycemia remains one of the contentious issues in contemporary neonatology[6,8,10,37,106-109], individual studies included in this review used different definitions of hypoglycemia ranging

from <1.1 mmol/l to <2.8mmol/l. The variation in the definition of hypoglycemia has an important implication on the predictive power of individual studies. The standard of care in most neonatology units involves close surveillance if the plasma glucose concentration is less than 2.2 mmol/l.[40,73,110-116] Second, mothers included in this review were diagnosed with diabetes. However, there was variation in the type of diabetes. The review included mothers with T1D, T2D, GDM, which are commonly recognized.[37, 106] Sarkar *et al.*[91] pointed out that the incidence of hypoglycemia and the associated risk factors may vary based on the specific type of diabetes. Third, about 65% of studies identified in the review were observational studies that used existing data collected as part of the standard of care (i.e. not for research purpose). In this regard, collecting prospective data or using national registry data may have provided more consistent predictors of hypoglycemia. Fourth, individual studies used different measurements of blood glucose. Although more than 76% of studies specified their blood glucose measurement methods, variations in these methods, measurement time, and place (laboratory vs. bedside) may have affected the accuracy of blood glucose measurement. Similarly, a recent systematic review identified 18 studies that examined neonatal hypoglycemia and its relationship to neurodevelopmental outcomes found a higher rate of heterogeneity among studies.[43] In our study, we also found major clinical heterogeneity in patient characteristics, measurement of hypoglycemia, design, and quality. As a result, statistical pooling of result to conduct a meta-analysis was not carried out.

Overall, the majority of the studies in our review were observational in design, which makes an inference of causality difficult, especially when different protocols were followed to measure, handle, and analyze blood sampling. Less than a third of the studies used a prospective design to minimize errors associated with measuring exposure. Key limitations include the

possibility of publication bias. As our review found both positive and negative results, publication bias may not be a great concern for the current review. The fact that our systematic review included studies only written in English may be another limitation. However, previous studies have shown that language restrictions in systematic reviews have minimal effect on the results.[117,118] The fact that 47 percent of studies did not report a laboratory measurement for confirmation of neonatal hypoglycemia and the lack of generally acceptable definition of neonatal hypoglycemia may have affected the proper direction of the outcome. However, as all studies followed a written clinical protocol in the management of hypoglycemia, the bias associated with laboratory confirmation is not differential.

Conclusions and Recommendations for Future Research

In summary, there is evidence supporting the clinical importance of giving attention to infants of diabetic mothers. Irrespective of the type of diabetes, infants of diabetic mothers have a higher risk of developing hypoglycemia compared to those born to mothers without diabetes. However, the studies included in this review mainly focused on the clinical characteristics of the infants and mothers. Future research should also focus on identifying other factors that may increase the risk of neonatal hypoglycemia such as neighborhood and institutional characteristics including, genetics, socioeconomic status, and disparities in health care delivery. This can be accomplished by taking the following four steps:

1. Defining neonatal hypoglycemia using the multiple clinical cut-of-points to identify the most salient risk factors.
2. Using large population based national registry database that is developed to facilitate the conduct of analyses pertaining to neonatal complications will help to obtain adequate comparison groups.

3. Stratifying the mother's diabetes type to identify the significance of T1D, T2D, and GDM on the risk of developing neonatal hypoglycemia.
4. Using multilevel statistical models to incorporate the individual and contextual characteristics of infants and mothers.

Table II.1. Description of Included Neonatal Hypoglycemia Studies

Author (s) (Year)	Design, *N*	Location	Patients Clinical Characteristics	Mother's Diabetes Type	Definition of Hypoglycemia, mmol/l/ mg/dl	Glucose Measurement Method (infant, mother)	Outcome Measured (hrs after birth)	Risk Factors Assessed
Agrawal, et al., 2000	Prospective cohort, 38	Australia	38 term infants of well-controlled diabetic, ≥37 wk gestation, 5 pre-existing diabetes, 35 GDM, 16 managed on insulin, 17 on diet	GDM	<2/36	Hexokinase; QIDTM	0.5, 1, 2	UBCG, RDS, BW
Majeed et al., 2011	Prospective Cohort, 150	Malaysia	139 GDM (76.7% diet control, 23.3% insulin), 11 pre-existing	GDM	≤2.6/47	NS, BioRad D-10	3	HbA1c
Bollepalli, et al., 2010	Retrospective Cohort, 229	U.S.	302 singleton, asymmetric LGA (63), symmetric LGA (67), asymmetric non-LGA (30), symmetric non-LGA (142)	T1D	<1.1/20	NS; Ames Dextrometer	NS	HB, AC, RD, PC
Ferrara, et al., 2007	Nested Case–Control, 2444	U.S.	1560 infants with neonatal complications, 884 control infants	GDM	<2.2/40	NS; Hexokinase	NS	MS, HB

Table II.1.Continued.

Author (s) (Year)	Design, *N*	Location	Patients Clinical Characteristics	Mother's Diabetes Type	Definition of Hypoglycemia, mmol/l/ mg/dl	Glucose Measurement Method (infant, mother)	Outcome Measured (hrs after birth)	Risk Factors Assessed
Flores-le Roux , et al., 2012	Prospective Cohort,190	Spain	190 infants, 39.3 wk mean gestational age; 3349 mean birthweight	GDM	Normal (>2.5/45), Mild (2.2/40-2.4/43), Moderate (1.6/29-2.1/38), Severe (<1.6/29)	Chromogen Reagent Strips; NS	1, 2, 4, 8, 12, 18, 24	PBMI, IG, GA, IL, CD, BW, LGA, AC, UCPH
García-Patterson, et al., 2012	Retrospective Cohort, 2092	Spain	2029 NH infants and 63 non-NH infants; 2029 pregnancies of women with GDM	GDM	<2.22	Cornblath criteria; NS	48	GA, CBG, HbA1c, IT, BMI, WDP, MP, NG
Das et al., 2009	Retrospective cohort, 305	U.S.	305 singleton neonates with a birthweight of ≥4000 g	GDM	<2.8/50	NS	NS	RDS, BI, CH, HS,
Maayan-Metzger et al., 2014	Retrospective cohort, 576	Israel	576 term infants, 37–42 wk gestation, non-complicated vaginal delivery	GDM-A1, GDM-A2, IDDM	(>2.6/47), Mild (2.2/40-2.5/45), Moderate (1.7/31-2.1/38), Severe (<1.7/31)	Glucometer Elite XL; NS	1, 2, 4, 6, 8	AGA, SGA, LGA, CD, MA, MH, MSAF

Table II.1.Continued.

Author (s) (Year)	Design, *N*	Location	Patients Clinical Characteristics	Mother's Diabetes Type	Definition of Hypoglycemia, mmol/l/ mg/dl	Glucose Measurement Method (infant, mother)	Outcome Measured (hrs after birth)	Risk Factors Assessed
Ryan et al., 2012	Retrospective cohort, 274	Canada	55 T1D, 55 T2D, 164 GDM	GDM, T1D, T2D	< 2/26	Capillary Blood Glucose; NS	Hourly	MBG
Sarkar et al., 2003	Prospective cohort, 160	U.S.	Infants born at ≥36 wk to women with GDM (class Al) over a period of 16 months; Infants born at ≥36 wk to nondiabetic women	GDM-A1	< 2.2/40	glucose oxidase; NS	0.5-1, 3	BW, GA, AC, MC, HbA1c
Taylor, et al., 2002	Retrospective Cohort, 107	UK	12.9 years of average duration of Type-1 Diabetes; 44 primigravidas	T1D	< 2.5/45	Yellow Springs	NS	MC
Tundidor, et al., 2012	Retrospective Cohort, 2299	Spain	Singleton pregnancies of women with GDM; < 22 wk gestation	GDM	< 2.6/47	NS	NS	PB, AS, LGA, SGA, OT, JD, CM, RDS, PT, HC, PM

Table II.1.Continued.

Author (s) (Year)	Design, *N*	Location	Patients Clinical Characteristics	Mother's Diabetes Type	Definition of Hypoglycemia, mmol/l/ mg/dl	Glucose Measurement Method (infant, mother)	Outcome Measured (hrs after birth)	Risk Factors Assessed
VanHaltren et al., 2013	Retrospective Cohort, 326	Australia	39 wk average Gestation; 3300 g. average birth weight; 15% LGA infants	GDM, T1D, T2D	< 2.6/47	Automated bench top blood gas; NS	0, 4	MI, TDM, HbA1c, BGL, GA, PM, BW
Mitrovic et al., 2014	Retrospective cohort, 156	Serbia	94 mothers with GDM, 48 T1D, 14 T2D; 106 controls	GDM, T1D	NS	NS	NS	AS, BW, GA,CD, PE
Persson, et al., 2012	Prospective cohort study, 3517	Sweden	3517 singletons, 32–43 wk gestation	T1D	< 2.6/47	NS	6	AS, BT, ARD, HB
Ramos, et al., 2012	Retrospective Cohort, 385	U.S.	Singleton pregnancies diagnosed with GDM b/n 12 & 34 wk (191), T2D (51)	GDM, T2D	< 2.5/45	Sure Step Flexx Glucose Meter; NS	0.5	PI, GA, CD, MA, MOGCT, CD

UCBG, umbilical cord blood glucose; RDS, respiratory distress syndrome; BW, birthweight; NS, not stated; HbA1c, glycated hemoglobin; HB; hyperbilirubinemia; AC, acidosis; PC, polycythemia; MS, macrosomia; GA, gestationalage; IT, insulin treatment; BMI, body max index; WDP; weight during pregnancy; MP, multiple pregnancy; NG, newborn gender, BI, birth injury; CH; cephalhaematoma, HS, hospital stay; CD, Cephalhaematoma; CD, Cesarean Delivery; MA, Maternal Age; MH, Maternal Hypertension; MSAF, meconium-stained amniotic fluid; AS, apgar score; PE, pre-eclampsia; BT, birth trauma; ARD, acute respiratory disorders; PI, ponderal index, MOGCT, maternal oral glucose challenge test; PBMI; Pregestational BMI; IG, insulin in gestation, IL, insulin in labor; UCPH; umbilical cord venous pH; MBG, maternal blood glucose, MC, microsomia; PT, polycythemia; HC, hypocalcaemia; PM, perinatal mortality; CM, congenital malformation; OT, obstetric trauma; JD, jaundice; PB, preterm birth; MI maternal insulin; TDM, type of gestational diabetes; PM, prematurity

Table II.2. Results of Included Studies of Hypoglycemic Neonates Born from Diabetic Mothers

Author (s) Years	Main Results
Agrawal, et al., 2000	Hypoglycemia in 18 (47%) infants developed during the first 2 h of life. There was no difference in the cord blood glucose levels between infants with or without hypoglycemia. Infants of mothers with diabetes diagnosed prior to 28 weeks gestation were at a higher risk of developing hypoglycemia (OR: 7.2, 95% CI: 1.3–40.7). Hypoglycemic infants were of significantly higher birthweight (3681) compared to normal infants (3160).
Majeed et al., 2011	There were 16 neonates who were hypoglycemic at delivery. The area under the Receiver Operator Characteristics (ROC) curve for predicting neonatal hypoglycemia was 0.997 with a 95% CI of 0.992 to 1. The optimal threshold value for HbA1c in predicting NH was 6.8%.
Bollepalli, et al., 2010	Asymmetric LGA infants had 3.5 (95% CI: 1.4, 8.7), 2.2 (95% CI: 1.2, 4.2), and 3.2 (95% CI, 1.7, 5.9) fold greater odds of hypoglycemia, hyperbilirubinemia, and composite morbidity, respectively, compared with symmetric non-LGA infants.
Ferrara, et al., 2007	A total of 486 with infants with hypoglycemia, 488 with macrosomia, and with hyperbilirubinaemia were identified. Women with GDM by ADA criteria had an increased risk of having an infant with hypoglycemia (OR: 2.61, 95% CI: 0.99–6.92), macrosomia (OR: 3.40, 95% CI: 1.55–7.43), or hyperbilirubinaemia (OR: 2.22, 95% CI: 0.98–5.04) compared to healthy control infants.
García-Patterson, et al., 2012	The rate of hypoglycaemia in neonates was 3% (63). Maternal pre-pregnancy BMI of ≥25 kg/m^2 was an independent predictor of hypoglycaemia irrespective of potential intermediate variables being included in the model (OR: 2.11, 95% CI: 1.10–4.03) or without (OR: 2.66, 95% CI:1.44–4.92).
Das et al., 2009	The incidence of hypoglycemia among IDMs was 56.1% compared to non-IDMs 28.6%. There was significantly more hypoglycemia among the group weighing >4500 g compared to the group weighing 4000–4499g. Compared to IDMs, non-IDMs were born later (40 vs 38 wk), were more likely to be delivered vaginally (70% vs 34%), and had a higher incidence of birth injury than IDMs (8% vs 2.4%).
Maayan-Metzger et al., 2014	Among the neonates in the study group, 29 (36.7%) had at least one hypoglycemia value of <47 mg/dl, and 8 (10.1%) had a value of <40 mg/dl in the first 8 hours of life. After controlling confounding factors such as birth weight, delivery number, and grasp evaluation only lower cord blood glucose significantly predicted hypoglycemia for each decrease of 10 mg/dl (OR: 2.11, 95% CI: 1.1–4.03).

Table II.2. Continued.

Author (s) Years	Main Results
Mitroviu et al., 2014	The incidence of neonatal hypoglycemia was 52% in mothers with Type 1 diabetes and 16.5% in mothers with Type 2 diabetes or GDM. The incidence neonatal morbidities such as hypoglycemia, pathological jaundice, and other neonatal pathologies at birth, was statistically significantly higher and Apgar scores after 1 minute and after 5 minutes were statistically significantly lower in the mothers with diabetes (type 1 & 2) compared to the healthy women.
Persson et al., 2012	Neonatal morbidities were significantly more frequent in LGA compared to AGA infants. The proportions of preterm births and girls were significantly higher in LGA infants (44% preterm and 52% girls) compared with AGA infants (30% preterm and 47% girls) born to women with Type 1 diabetes. The risks of hypoglycemia were comparable between P-LGA and D-LGA infants. No significant difference in risk was found between AGA and P-LGA and D-LAG.
Ramos et al., 2010	The incidence of hypoglycaemia was 18% (44/242). The incidence was significantly higher in those requiring pharmacotherapy (25% vs. 3%). The frequency of hypoglycaemia between the glyburide and insulin-treated pregnancies did not differ significantly (23% vs. 27%). The frequency of hypoglycaemia was statistically associated with birth weight, macrosomia, and ponderal index. Ponderal index was the strongest predictor of hypoglycaemia (OR: 5.59, 95% CI: 1.34–23.25).
Flores-le Roux et al., 2012	A total of 23 (12.1%) mild, 20 (10.5%) moderate and 5 (2.6%) severe hypoglycemia were observed. Hypoglycemic infants were more frequently LGA (29.3% vs 11.3%), had lower umbilical cord pH (7.28 vs 7.31) and their mothers had more frequently been hyperglycemic during labor (18.8% vs 8.5%). Pakistani origin (OR: 2.94; 95% CI: 1.14 7.55) and umbilical cord venous pH (OR: 0.04, 95% CI: 0.261–0.99) were significantly and independently associated with hypoglycemia in multivariate analysis.
Ryan et al., 2012	The NH rate was 7.3% (4.9% in GDM mothers and 10.9% of mothers with pre-existing diabetes). The insulin-glucose infusion was used in 47% of women with T1D, T2D, and GDM requiring ≥ 0.5 units/kg/day of insulin during pregnancy and in 8% of women with GDM treated by diet or < 0.5 units/kg/day of insulin. The overall rate of maternal hypoglycaemia was low (6.6% with blood glucose ≤ 3.5 mmol/L and 1.5% ≤ 3.0 mmol/L) pre-delivery; 13.9% of women had a blood glucose level ≥ 7.0 mmol/L. Standardized management for diabetic women in labour using an intravenous insulin-glucose protocol was effective in achieving stable maternal blood glucose levels with low rates of neonatal hypoglycaemia.

Table II.2. Continued.

Authors (s) Years	Main Results
Sarkar et al., 2003	The incidence of hypoglycemia was 4.3% in the GMD-A1 group compared to the control, 4.4%. Neonatal morbidity in infants born to GDM-A1 women is similar to that seen in infants of nondiabetic women. Unlike infants of insulin-dependent diabetic and insulin requiring GDM women, infants born to GDM-A1 women at 36 weeks of gestation or more were not at increased risk of developing hypoglycemia, hypocalcemia, hypomagnesemia, polycythemia, hyperbilirubinemia, birth trauma, or birth asphyxia. Infants born at 36 weeks or more gestation to class A1 GDM women can be managed like any other normal full-term infant born to a nondiabetic woman.
Taylor, et al., 2002	Hypoglycemia correlates with maternal hyperglycemia in labor, not with HbA1c during pregnancy. Blood glucose was less than 2.5 mmol/l in 50 neonates and was less than 2.0 mmol/l in 18 neonates. Maternal blood glucose control in pregnancy had no bearing on the incidence of NH, but maternal blood glucose during labor influenced neonatal blood glucose if over 8 mmol/l.
Tundidor, et al., 2012	Male sex was an independent predictor of neonatal hypoglycemia (OR: 2.13) and CS (OR: 1.48). As to neonatal hypoglycaemia, intravenous glucose was required in 16.7% of infants (7.4% in female vs 24.2% in male fetuses; NS). The increased risk of neonatal hypoglycemia in male fetuses of mothers with GDM is also the most relevant result in terms of clinical practice, advising an increased awareness of neonatal hypoglycemia in these newborns.
VanHaltren et al., 2013	Hypoglycaemic episodes occurred in 109 (33.4%) infants. Macrosomia was present in 15% of the infants. Maternal diabetes Type, HbA1c, prematurity, macrosomia, and temperature instability were identified as risk factors for neonatal hypoglycaemic.

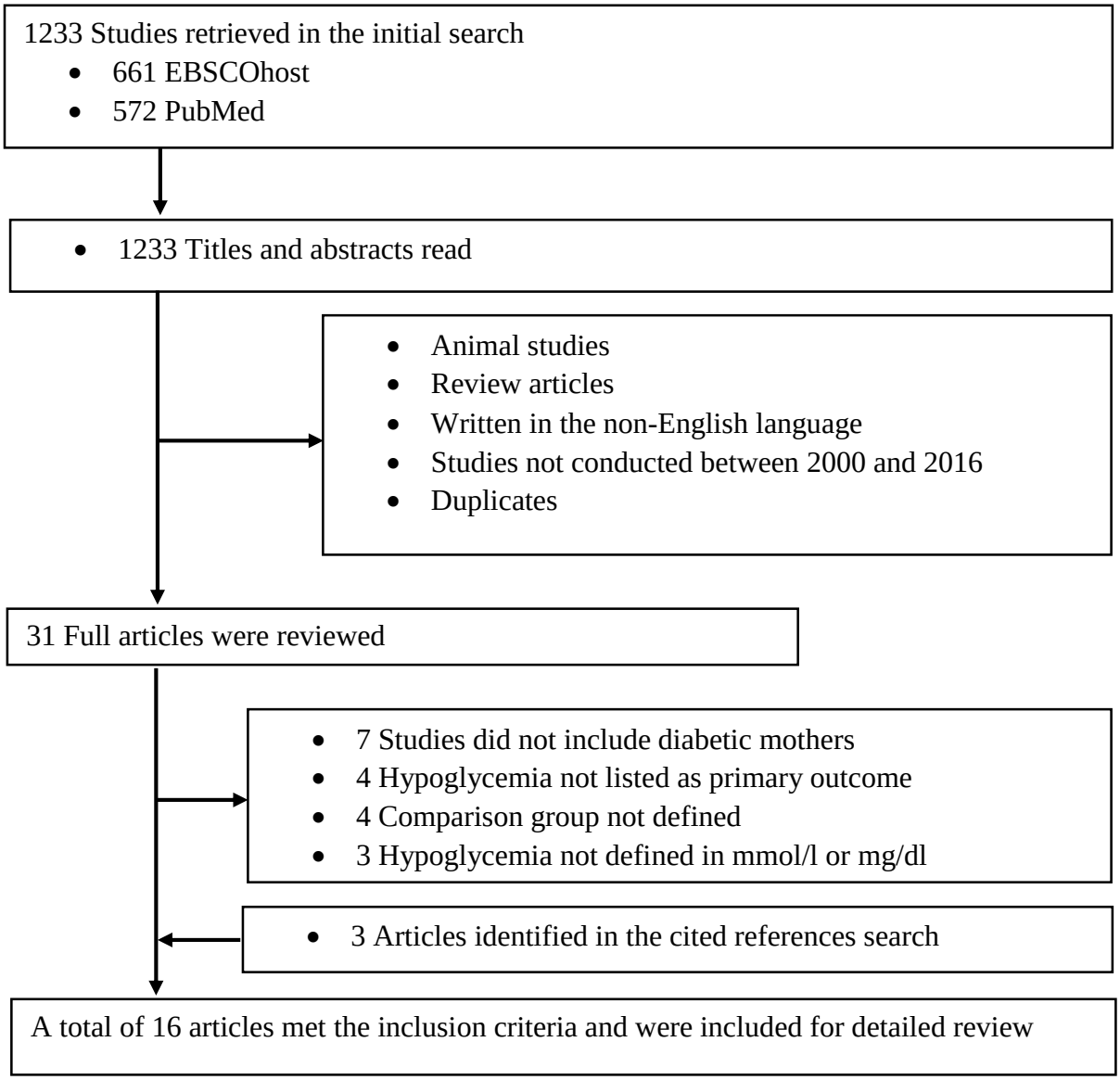
Table II.3. Description of Methodological Quality Assessment

Items	Agrawal et al. (2000)	Majeed et al. (2011)	Bollepalli et al. (2010)	Ferrara et al. (2007)	Garcia-Patterson et al. (2012)	Das et al. (2009)	Maayan-Metzger et al. (2014)	Mitroviu et al. (2014)
1.Study design	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
2.Setting	Yes	Yes	Yes	Yes	No	No	No	No
3.Participants	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes
4.Variables	Yes	Yes	Yes	Yes	No	No	No	No
5.Measurement	Yes	No	No	Yes	Yes	No	Yes	No
6.Bias	No	No	No	No	No	No	No	No
7.Study size	No	No	No	No	No	No	No	No
8.Statistical methods	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No
9.Discriptive data	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
10.Outcome data	No	No	No	Yes	No	Yes	No	No
11.Main results	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
12.Key Result	Yes	Yes	Yes	Yes	Yes	No	No	No
13.Limitations	Yes	Yes	No	Yes	No	Yes	No	No
14.Interpretation	Yes	Yes	Yes	Yes	No	No	No	No
15.Generalizability	Yes	No	No	Yes	No	No	No	No
Percentages of Yes (%)	*12/15= 80.00*	*10/15= 66.66*	*9/15= 60.00*	*13/15= 86.66*	*7/15= 46.66*	*6/15= 40.00*	*6/16= 40.00*	*4/15= 26.66*

Table II.3. Continued.

Items	Persson et al. (2012)	Ramos et al. (2010)	Flores-le Roux et al. (2012)	Ryan et al. (2012)	Sarkar et al. (2003)	Taylor et al. (2002)	Tundidor et al. (2012)	VanHaltren et al. (2013)
1.Study design	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
2.Setting	No	No	Yes	No	Yes	No	No	No
3.Participants	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes
4.Variables	Yes	Yes	Yes	Yes	Yes	No	No	No
5.Measurement	No	No	Yes	No	No	No	No	No
6.Bias	Yes	No	Yes	No	No	No	No	No
7.Study size	Yes	No	No	No	Yes	No	Yes	No
8.Statistical methods	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes
9.Discriptive data	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
10.Outcome data	No	No	No	No	No	No	Yes	No
11.Main results	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No
12.Key Result	Yes	No	Yes	No	Yes	No	No	No
13.Limitations	Yes	No	Yes	No	Yes	No	No	Yes
14.Interpretation	Yes	Yes	Yes	No	Yes	No	No	Yes
15.Generalizability	Yes	No	Yes	No	Yes	No	No	No
Percentages of Yes (%)	*12/15= 80.00*	*7/15= 46.66*	*13/15= 86.66*	*5/15= 33.33*	*12/15= 80.00*	*4/15= 26.66*	*7/15= 46.66*	*6/15= 40.00*

Figure II.1. Selection Process for Including Studies in the Systematic Review



CHAPTER III

PROJECT II: PREDICTORS OF HOSPITALIZATION COST IN INFANTS WITH HYPOGLYCEMIA: ANALYSIS OF HCUP KID'S DATABASE

Introduction

Neonatal hypoglycemia is a common metabolic abnormality in newborns due to inability to maintain glucose homeostasis.[4,84] Throughout gestation, mothers provide all the glucose for their fetuses via facilitated diffusion across the placenta according to a maternal-to-fetal glucose concentration gradient.[6] The disruption of this process can lead to several acute and chronic illnesses. The most common symptoms of neonatal hypoglycemia are shakiness, tachycardia, lethargy, and temperature irregularities.[23] In the presence of these symptoms, neonatal hypoglycemia is defined as capillary plasma glucose of less than 46 mg/dl (2.6 mmol/l).[8,23] Several clinical conditions could be associated with neonatal hypoglycemia that could affect glucose homeostasis including asphyxia, congenital heart disease, decreased substrate availability as a result of birth defects, prematurity and fetal growth restriction, islet cell hyperplasia, and Beckwith-Wiedemann Syndrome.[15,17,18,20,21] Prolonged neonatal hypoglycemia may also cause neuroglycopenic signs such as seizures, coma, cyanotic episodes, apnea, respiratory distress, and hypothermia.[4]

Previous studies on this topic mainly focused on the clinical risk factors and analyses aimed at improving the management and care of neonatal hypoglycemia. However, the economic burden and overall hospital cost estimates has not been studied at the national level in the United States (US). Although not in neonates, the economic burden of hypoglycemia has been adequately addressed in adult populations[44-49]. This study sought to determine the overall hospital cost estimates in neonates with hypoglycemia and compare hospital cost in premature

and non-premature newborns. The study also sought to identify predictors of increased hospital cost.

Methods

This is a retrospective study based on the 2012 Kids' Inpatient Database (KID) developed by the Healthcare Cost and Utilization Project (HCUP) of the Agency for Healthcare Research and Quality (AHRQ).[54] The KID is the largest publicly available all-payer pediatric (≤20 years of age) inpatient care database in the United States. The database is a sample of pediatric discharges from all community, non-rehabilitation hospitals in 44 participating States. Systematic random sampling is used to select 10% of uncomplicated in-hospital births and 80% of other pediatric cases from each participating state. The 2012 KID database includes 4179 hospitals with 3,195,782 pediatric discharges. HCUP categorize hospital regions as northeast, mideast, south, and west. Hospital ownership, teaching status, location, bed size, and other important hospital characteristics were also included in the database. In total, 70 children's hospitals (400,835 pediatric discharges) and 4,109 hospitals that admit all patients (2,794,947 pediatric discharges) were included in the 2012 database. As we are interested only in neonates, this analysis is limited to uncomplicated and complicated in-hospital births.

For the purpose of our analysis the inpatient core file, the hospital file, and cost-to-charge ratios file of the KID 2012 database were used. Neonates with hypoglycemia (775.6) were identified using the 9th version of the international classifications of diseases (ICD-9-CM). The outcome variable was identified by converting the total hospital charge to hospital cost estimates (Hospital Costs = Cost-to-Charge Ratios*Total Charges).[78] Using the distribution of total hospital cost estimates we categorized hospital cost into increased hospital cost estimates (> 75th percentile) and lower hospital cost estimates (≤ 75th percentile).

Neonatal comorbidities associated with hypoglycemia were defined as a dichotomous variable using ICD-9-CM codes. In this respect, the presence of any comorbidities associated with neonatal hypoglycemia such as jitteriness (796.9), hypotonia (781.3), lethargy (799.22), apnea (786.03), tachypnea (786.06), poor feeding (783.3), hypothermia (991.6), sepsis (995.91& 771.81), seizures (345.x), neurodevelopmental (315.x) deficits were used to create a dichotomous variable that indicates the morbidity status of newborns. In addition, demographic information (age, sex, and race), region of hospitals (northeast, midwest, south, west), hospitals teaching status, bed-size category (small, medium, large), admission date (weekend versus weekdays), length of hospital stay (LOS), number procedures performed during hospitalization (NPR), number of chronic conditions during hospitalization, expected primary payer, and in-hospital mortality were extracted for the purpose of the current analysis. Hospitalization for hypoglycemic neonates was categorized into premature and non-premature using the Diagnosis Related Groups version 24 (DRG24) codes (386-388). DRG24 is assigned by the Centers for Medicare & Medicaid Services (CMS) DRG Grouper algorithm during HCUP processing and it has been available since 2006.[54]

We used the Kolmogorov-Smirnov test (KS-Test) to assess normality for continuous variables. Groups were compared using the Wilcoxon-Mann-Whitney test for continuous variables and the $\chi 2$ test for categorical variables. For continuous variables data were presented in median and interquartile range (IQR). Whereas categorical variables were presented as numbers (n) and percentages (%). Odds ratios (OR) for increased hospital cost estimates were determined by using bivariate and multivariate logistic regression. All variables that were significantly associated with increased cost ($P < 0.05$) were included in the multivariable logistic

regression analysis. We used this stringent criterion for inclusion in the model because of the large sample size.

A $P < 0.05$ was considered statistically significant for all tests. SAS® version 9.3 was used for the analysis (Institute Inc., Cary, NC, USA). In assessing the calibration of our model, we used the Receiver Operating Characteristics (ROC) curve to calculate c statistic and the Deviance – Pearson (D-P) goodness of fit statistics.[119,120] The two model evaluation measures carried out in this study should provide enough assurance regarding the accuracy of our model.

Results

A total of 3,195,782 hospital discharges were included in the 2012 KID HCUP database, from which 1,107,573 were in-hospital births. From the total in-hospital birth, we were able to identify 50,650 neonates with hypoglycemia (5%). In 2012, the total hospital cost in neonates with hypoglycemia was 821 M$. Since the total cost for in-hospital births was 7,692 M$, hospital cost in neonates with hypoglycemia represents 11%. Figure III.1 indicates the relative proportion the cost for premature (73%: 602 M$) and non-premature (27%: 219 M$) neonates. The median cost estimates in premature and non-premature neonates were $12,755 ($4,550-$30,339) and $2,360 ($1,153-$3,736), respectively. On the other hand, Figure III.2 represents the distribution of hospital cost estimates by primary payer which are divided into Medicaid (50%: 410 M$), private insurance (44%: 364 M$), Self-pay (1%: 10.7 M$), and other (5%: 36.2 M$). In addition, Figure III.3 indicates that the per capita cost estimates among the four United States regions, that are northeast (19 K$), Midwest (15 K$), South (14 K$), and West (18 K$). Total cost estimates that exceed the 75th percentile ($13,575) was defined as excessive cost associated with hospital discharge.

Table III.1 represents characteristics of neonates with hypoglycemia that were categorized into two subgroups. We observed that 40% (n=20, 588) of neonates were premature. Among infants included in the study, 55% were White, 17% Black, 16% Hispanic, 4% Asian/Pacific and 1% Native Americans while 57% and 43% of the neonates were male and female. The median values for premature and non-premature neonates were as follows: NPR 2 (IQR 1-4) and LOS 11 (5-24) and NPR 2 (IQR 0-2) and LOS 3 (2-5), respectively. In 2012, the prevalence of hypoglycemia among in-hospital births in the United States was 5 % (n=50,650).

The results from our multivariate analysis to determine factors associated with increased cost estimates among hypoglycemic neonates are presented in Table III.3. Increased costs were observed, when more than five procedures were performed during the same hospitalization (OR 10.13, 95% CI 8.67-11.83, $P < 0.0001$), when hospital bed size were between 100 and 300 (OR 1.37, 95 % CI 1.16-1.61, $P = 0.0002$) and ≥ 400 (OR 1.65, 95% CI 1.41-1.92, $P < 0.0001$), when hospital length of stay exceeds 15 days (OR 44.97, 95% CI 41.49-48.73, $P < 0.0001$), when hospitals have teaching status (OR 1.97, 95% CI 1.82-2.13, $P < 0.0001$), in the case of chronic conditions (OR 2.46, 95 % CI 2.27-2.66, $P < 0.0001$), comorbidity (OR 2.11, 95% CI 1.90-2.35, $P < 0.0001$), prematurity (OR 2.39, 95% CI 2.20-2.60, $P < 0.0001$), and death (OR 2.95, 95% CI 2.13-4.09, $P < 0.0001$). In the unadjusted analysis, all variables included in the models were independently associated with increased hospital costs (Table III.2).

The area under the ROC curve (0.95, 95% CI 0.948-0.953) indicated the predictive accuracy of the multivariate model. In addition, the results from the D-P goodness of fit (d= 3820, df =3722) also expressed that the values for deviance (d) are not much larger than their degrees of freedom, suggesting that the fitted model cannot be rejected and leads to the conclusion that the model fits well.[119]

Discussion

Our analysis of the 2012 HCUP KID database shows that hospital cost estimates in neonates with hypoglycemia consumed 11% of the resources associated with hospital births. We determined a 5% prevalence of neonatal hypoglycemia among in-hospital births in the U.S during the year 2012. We also determined that medium and large hospital bed sizes, LOS, NPR, teaching hospitals, composite neonatal comorbidities, prematurity, occurrence of chronic conditions, and mortality were independently associated with increased hospital cost estimates in neonates with hypoglycemia.

Previous studies have focused on estimations of the economic cost of hypoglycemia in the adult population.[44-49] To our best knowledge, this is the first study providing an empirical estimate of the hospital cost of neonatal hypoglycemia at the national level. It is worth noting that 100% of mortality and higher morbidity (51%) occurred in the non-premature group. As premature neonates are usually treated in neonatal intensive care units that provide around-the-clock care, non-premature babies appear to be prone to mortality and various hypoglycemia related comorbidities. Furthermore, since premature neonates are more likely to be delivered by caesarian section, non-premature neonates are at increased risk for serious birth related morbidities such as birth trauma.[70] This result is consistent with previous studies[16,41,77,121] in that neonates with asymptomatic hypoglycemia may easily be neglected of proper care which may lead to acute comorbidities and even death. As the majority of hypoglycemic cases are asymptomatic, enough emphasis should be given this subgroup.

At this juncture, an explanation of the cost-to-charge ratios (CCRs) is warranted. The HCUP KID contains data on total charges for each hospital in the databases. This charge information represents the amount that hospitals billed for services but does not reflect how

much hospital services actually cost.[54] Cost information was obtained from the hospital accounting reports collected by the CMS. Statistical imputation for missing values and internal validation studies were carried out to enhance the accuracy of the CCRs.[75,77] Most hospital-based studies use total charge as a proxy measurement for actual cost.[53] This may lead to drawing unwarranted conclusions about economic efficiency and hospital resource utilizations.[53] To maximize the accuracy of the cost estimation, our study used actual cost by converting the total hospital charge to hospital cost estimates using CCRs.

We recognize that there are some limitations associated with this study. The ICD-9-CM classification system is imperfect for case identification, as it was created for reimbursement rather than research purposes. As a result, important clinical conditions pertinent for neonatal outcome research may have been missed. Because KID 2012 lacks individual identifiers for states, we were not able to conduct comparative analysis among various states. However, despite the potential limitations, the HCUP KID database is the largest validated and publicly available all-payer pediatric inpatient care database[54] that can be used to evaluate national cost estimates, resource utilization, and economic burden of hospitalization in the pediatric population.

Conclusion

This study demonstrated that neonates with hypoglycemia consumed 11% of resources associated with hospital births while accounting for only 1.5% of hospitalization. We also determined that hospital length of stay, hospital bed size, teaching hospitals, number of procedures performed during hospitalization, chronic conditions, comorbidity, prematurity, and in-hospital mortality were independently associated with increased hospital cost. Our results also suggested that non-premature hypoglycemic babies should be provided with more care to reduce acute comorbidities and death during hospitalization

Table III.1. Characteristics of Neonates with Hypoglycemia by Prematurity Status

Variables	Premature (*N*= 20,588) (40%)	Non-Premature (*N*=30,062) (60%)	Total (*N*= 50,650) (100%)	P Value
Gender n, (%)				<.0001
Male	10,781(37.11)	18,269 (62.89)	29,050 (57.38)	
Female	9,800 (45.42)	11,778 (54.58)	21,578 (42.62)	
Race n, (%)				<.0001
White	9,826 (38.88)	15,448 (61.12)	25,274 (55.40)	
Black	3,599 (47.11)	4,041 (52.89)	7,640 (16.75)	
Hispanic	2,893 (40.80)	4,197 (59.20)	7,090 (15.54)	
Asian/Pacific	714 (38.02)	1,164 (61.98)	1,878 (4.12)	
Native Americans	170 (38.99)	266 (61.01)	436 (0.96)	
Admission Day n, (%)				<.0001
Weekday	15,816 (39.51)	24,216(60.49)	40,032 (79.04)	
Weekend	4,772 (44.94)	5,846 (55.06)	10,618 (20.96)	
Hospital n, (%)				<.0001
Teaching	12,952 (44.64)	16,060 (55.36)	29,012 (57.28)	
Non-Teaching	7,636 (35.29)	14,002 (64.71)	21,638 (42.72)	
Bed Size n, (%)				<.0001
Small (1-99)	1,310 (30.83)	2,939 (69.17)	4,249 (8.39)	
Medium (100-399)	5,071 (39.19)	7,869 (60.81)	12,940 (25.55)	
Large (≥ 400)	1,4207 (42.46)	19,254 (57.54)	33,461 (66.06)	
Ownership n, (%)				<.0001
Private	15,161 (40.58)	22,200 (59.42)	37,361 (73.76)	
Public	5,427 (40.84)	7,862 (59.16)	13,289 (26.24)	
Morbidity n, (%)	2,982 (49.01)	3,102 (50.99)	6,084 (12.01)	<.0001
Mortality n, (%)	0 (0)	389 (100)	389 (0.77)	
NPR[#*]	2 (1-4)	2 (0-2)	4 (2-11)	<.0001
LOS days [+*]	11 (2-24)	3 (2-5)	1 (0-3)	<.0001

[+]LOS, Hospital length of stay in days; [#]NPR, number of procedure. Data are presented in number (n) and percentage (%), or [*]Median and interquartile range (IQR)

Table III.2. Unadjusted ORs, 95% CIs, and P Values from Bivariate Logistic Regression Analysis Associated with Increased Cost Estimates (>75th Percentile)

Variables	Unadjusted OR	B (SE)	95% CI	P value
Female	1.20	0.19 (0.02)	1.16 1.26	<.0001
Black	1.65	0.50 (0.03)	1.55-1.74	<.0001
Hispanic	1.37	0.31 (0.03)	1.29-1.45	<.0001
Asian/Pacific	1.41	0.34 (0.05)	1.27-1.56	<.0001
Native Americans	1.10	0.10 (0.11)	0.88-1.38	0.3721
Weekend	1.14	0.14 (0.02)	1.09-1.20	<.0001
Medium (100-399)	1.91	0.65 (0.05)	1.74-2.10	<.0001
Large (≥ 400)	2.24	0.80 (0.05)	2.05-2.45	<.0001
Teaching Hospital	2.28	0.83 (0.02)	2.19-2.39	<.0001
LOS[+] >15 days	95.36	4.56 (0.03)	89.32-101.82	<.0001
NPR[#] >5	43.21	3.77 (0.05)	38.93- 47.96	<.0001
Chronic Condition	5.82	1.76 (0.02)	5.57-6.08	<.0001
Death	6.01	1.79 (0.11)	4.87-7.42	<.0001
Premature	8.95	2.19 (0.02)	8.53-9.38	<.0001
Morbidity	3.45	1.24 (0.03)	3.26-3.64	<.0001

OR, odds ratio; B, regression coefficient; SE, standard error; CI, confidence interval; [+]LOS, Hospital length of stay in days; [#]NPR, number of procedures

Table III.3. Adjusted ORs, 95% CIs, and P Values from Multivariate Logistic Regression Analysis Associated with Increased Cost Estimates (>75th Percentile)

Variables	Adjusted OR	B (SE)	95% CI	P value
Female	1.01	0.01 (0.09)	0.94-1.09	0.7439
Black	0.89	-0.12 (0.05)	0.8.0-0.98	0.0185
Hispanic	1.26	0.23 (0.05)	1.13-1.39	<.0001
Asian/Pacific	1.95	0.67 (0.09)	1.63-2.32	<.0001
Native Americans	1.57	0.45 (0.19)	1.09-2.28	0.0163
Weekend	1.04	0.04 (0.05)	0.95-1.14	0.3816
Medium (100-399)	1.37	0.31 (0.08)	1.16-1.61	0.0002
Large (≥ 400)	1.65	0.50 (0.08)	1.41-1.92	<.0001
Teaching Hospital	1.97	0.68 (0.04)	1.82-2.13	<.0001
LOS >15 days	44.97	3.81 (0.04)	41.49-48.73	<.0001
NPR >5	10.13	2.32 (0.08)	8.67-11.83	<.0001
Chronic Condition	2.46	0.90 (0.04)	2.27-2.66	<.0001
Death	2.95	1.08 (0.17)	2.13-4.09	<.0001
Premature	2.39	0.87 (0.04)	2.20-2.60	<.0001
Morbidity	2.11	0.75 (0.05)	1.90-2.35	<.0001

OR, odds ratio; B, regression coefficient; SE, standard error; CI, confidence interval; $^{+}$*LOS, Hospital length of stay in days;* $^{\#}$*NPR, number of procedures*

Figure III.1. Total Cost Estimates in Neonates with Hypoglycemia by Prematurity Status. Total Costs Are Expressed In Million US Dollars (M$) For Premature and Non-Premature Neonates with Hypoglycemia

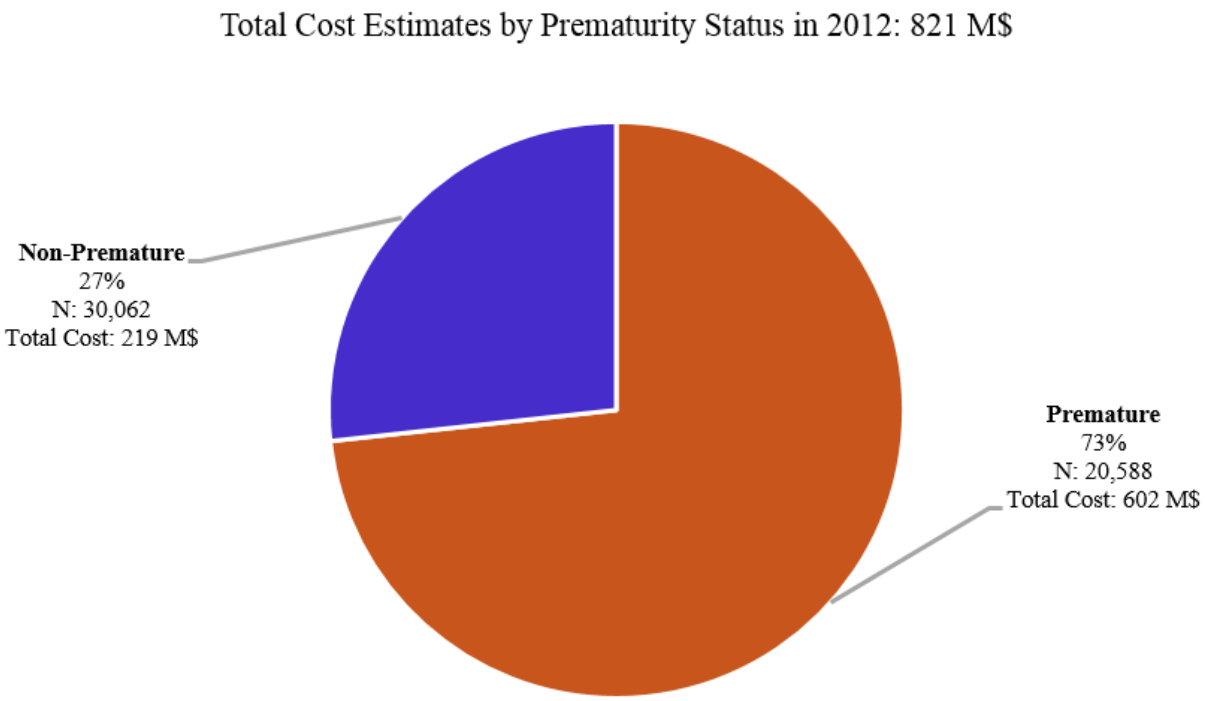


Figure III.2. Total Cost Estimates in Neonates with Hypoglycemia by Primary Payer. Total Costs Are Expressed In Million US Dollars (M$) and Divided Among Private Insurance, Medicaid, Self-Pay, and Other

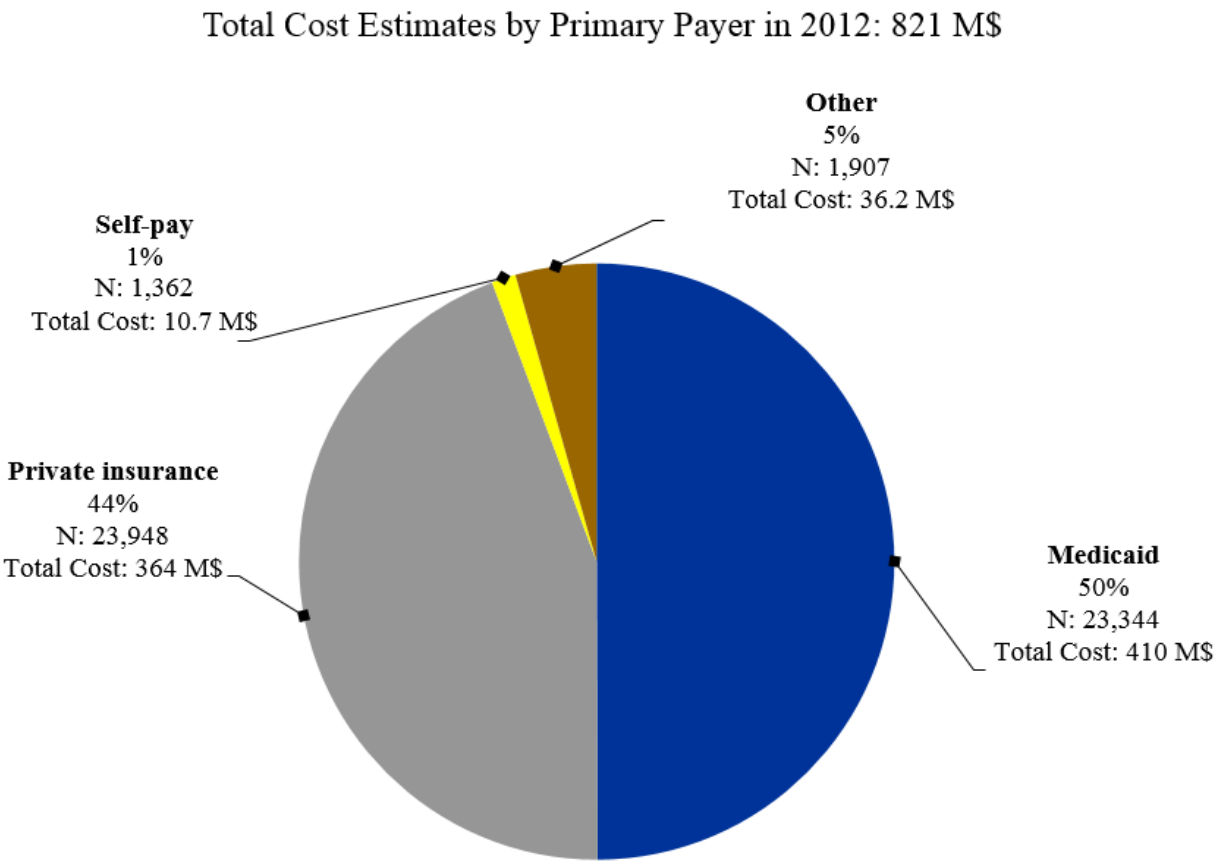
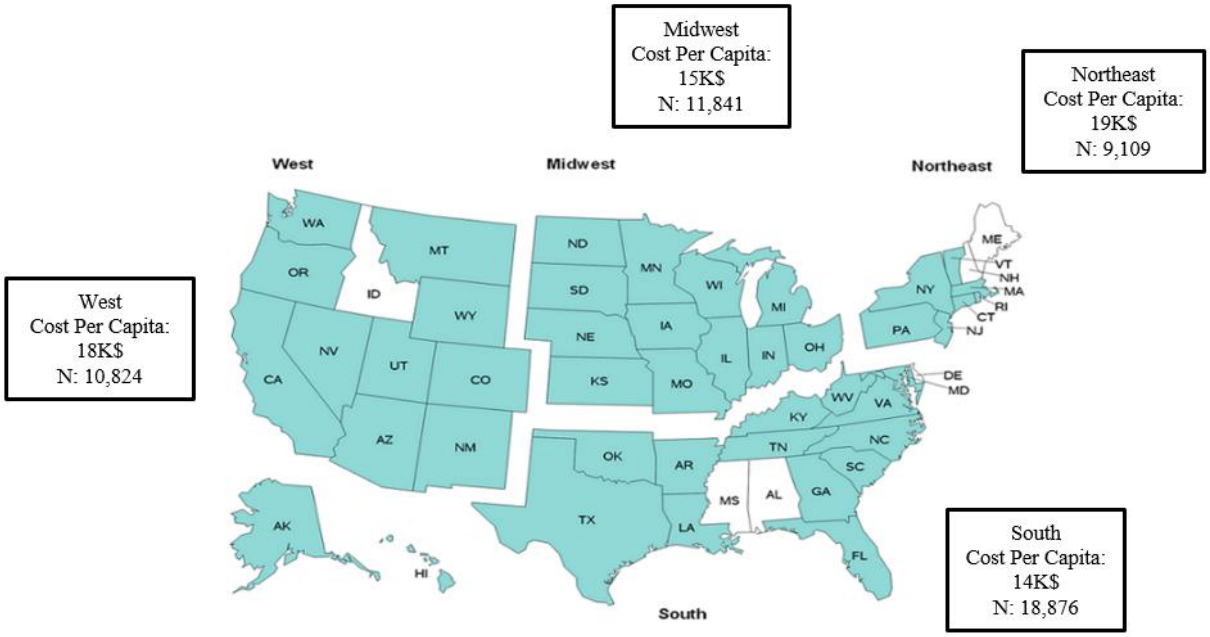


Figure III.3. Per Capita Cost Estimates in Neonates with Hypoglycemia by Region. Per Capita Costs Are Expressed In Thousand US Dollars (K$) For Four US Regions: Northeast, Midwest, West, and South



CHAPTER IV

PROJECT III: A MULTILEVEL MODELING ANALYSIS OF PREDICTORS OF NEONATAL HYPOGLYCEMIA IN DIABETIC AND NON-DIABETIC MOTHERS

Introduction

Neonatal hypoglycemia is the most common metabolic abnormality in infants and is associated with neurological damage and death.[4] Estimates for neonatal hypoglycemia are between 3% and 29% of all pregnancies in the United States.[122] As glucose is an essential primary substrate for the brain,[4,122] neurons, and glial cells are susceptible to hypoglycemia.[84] Neonates with hypoglycemia are prone to various acute[84] and chronic health problems.[43,123] In the short run, newborns may experience jitteriness, hypotonia, lethargy, irritability, apnea, tachypnea, poor feeding, hypothermia, and seizures.[55] Later in their life, they may experience a neurodevelopmental delay or even death.[55,124] Due to poor nutritional status, infectious diseases, and the lack of diagnostic facilities, neonatal hypoglycemia in resource poor countries has far more serious consequences for health.[124] The risk of developing hypoglycemia among infants born from diabetic mothers is even higher.[6]

For neonates to have a normal brain, adequate supply of glucose during infancy is crucial.[70] Therefore, the lack of this essential substrate at the early stage of growth may lead to various acute[122] and long term[43] life-threatening medical conditions. Hypoglycemia occurs in approximately 3-20% of neonates born to mothers with diabetes[6,55,124], with an estimated incidence rate of approximately 27% among infants born to women with diabetes compared to 3% among full-term healthy infants born to non-diabetic women.[35,36] Previous research on neonatal hypoglycemia[21,23,25,33,34,70,72,73,91,92,95,96,98-101] mainly focused on individual-level risk

factors such as poor maternal glycemic control, neonatal weight at birth, and gestational age at delivery as predisposing risk factors for the development of neonatal hypoglycemia in diabetic pregnancies. However, contextual risk factors such as neighborhood economic status, type of insurance, hospital characteristics, and regional variations were not considered in these studies.

Neonatal hypoglycemia is a highly preventable medical condition[71] and yet it poses a significant threat to the health of newborns. Due to lack of adequate knowledge about the potential individual and contextual risk factors, the prevention of neonatal hypoglycemia has been difficult.[57, 125] Therefore, considering these multilevel characteristics in assessing the determinants of neonatal hypoglycemia is necessary to understand the complex relationship among various influencing factors. In addition, since neonatal hypoglycemia is strongly associated with poor maternal health[33,72,73], the identification of the risk factors is important to improve the mothers' health through effective prevention measures that can reduce high-risk pregnancies.

The purpose of the current study was to construct multilevel models that include individual-level and contextual-level characteristics in order to predict neonatal hypoglycemia in diabetic and non-diabetic mothers. We hypothesized that infants born from diabetic mothers will have significantly higher chance of developing hypoglycemia compared to those born from non-diabetic mothers. The addition of the contextual-level factors was also expected to enhance the predictive power of the models. Addressing these issues using a large nationally representative database is necessary to guide the prevention and control of adverse health outcomes associated with hypoglycemia in these priority populations.

Materials and Methods

The current study used the 2012 Kid's Inpatient Database (KID) developed by the Healthcare Cost and Utilization Project (HCUP). The proposed research is a cross-sectional study that examines hospital discharges of newborn infants delivered after complicated or uncomplicated pregnancies.

The KID is the largest publicly available all-payer pediatric (≤20 years of age) inpatient care database in the United States. The 2012 KID database includes 4179 hospitals and 3,195,782 pediatric discharges. HCUP categorize hospital regions as northeast, mideast, south, and west. In addition to demographic and clinical measures, hospital ownership, teaching status, location, bed size, and other important hospital characteristics were also included in the database. In total, 70 children's hospitals (400,835 pediatric discharges) and 4,109 hospitals that admit all patients (2,794,947 pediatric discharges) were included in the 2012 database. As we are interested only in neonates, this analysis is limited to uncomplicated and complicated in-hospital births. Hospital discharges with missing, invalid, or inconsistent ages were excluded from the HCUP KID.

For sampling, pediatric discharges were stratified by uncomplicated in-hospital birth, complicated in-hospital birth, and all other pediatric cases. For an accurate representation of each hospital's pediatric case-mix, the discharges were sorted by State, hospital, diagnosis-related group (DRG), and a random number within each DRG. Then, systematic random sampling was used to select 10% of uncomplicated in-hospital births and 80% of complicated in-hospital births and other pediatric cases from each sampling frame hospital. To obtain national estimates, discharge weights were developed using the American Hospital Association universe as the standard. This is the first study that proposed to use a nationally representative database to identify risk factors and healthcare utilization outcomes associated with neonatal hypoglycemia.

Inclusion/Exclusion Criteria

Subjects were eligible to be included in the study if they were neonates (first 28 days after birth), had a diagnosis of hypoglycemia (ICD-9-CM=775.6), and were born in the 44 HCUP participating States in the year 2012. All other pediatric cases occurred in the United States community, non-rehabilitation hospitals were excluded from the study.

Variables

The current study included both individual and contextual level characteristics of neonatal hypoglycemia. International classification of diseases, 9th version (ICD-9-CM codes), Diagnostic Related Groups (DRGs), Clinical Classifications Software Category (DXCCS1-DXCCS25), and Clinical classification software category for all procedures (PRCCS1-PRCCS15) were used to extract the independent variables. The dependent variable, neonatal hypoglycemia, was extracted as dichotomous variables using the ICD-9-CM code 775.6. The complete list of codes used to identify variables are listed in Appendix A.

The individual characteristics included in the analysis were gender, race, prematurity, small-for-gestational age (birth weight <10th percentile), large-for-gestational-age (birth weight >90th percentile), mortality, addmission type (scheduled, non-scheduled), addmision day (weekend, weekday), indicator of emergecy service use, comorbidities including jitteriness, hypotonia, lethargy, irritability, apnea, tachypnea, poor feeding, hypothermia, sepsis, seizures, neurodevelopmental deficits. An indicator of maternal diabetes status (Type I, Type II, or Gestational), history of substance/alcohol abuse, and delivery mode (caesarian, normal) were included as individual characteristics associated with the mother.

Contextual variables such as region (Northeast, Midwest, South, West), insurance type (Medicare, Medicaid, Private insurance, Self-pay, No charge), median household income for

patient's zip code ($1-$38999, $39000-$47999, $48000-$62999, $63000+), admission season (January-March, April-June, July-September, October-December), hospital bed size (1-99, 100-399, ≥ 400), ownership (public, private), teaching status, and location (rural, urban) were included in the analysis.

Statistical Analysis

For the purpose of our analysis, the inpatient core file and the hospital file were used. All analyses were weighted to account for the complex probability sampling of the dataset and permit inferences regarding the risk factors for neonatal hypoglycemia. Descriptive and inferential statistics were performed taking complex survey design into consideration. Groups were compared using the Rao-Scott $\chi 2$ test for categorical variables. Values were presented as numbers (n), percentages (%), and odds ratios (OR).

Hierarchical logistic regression models were constructed to simultaneously examine individual and contextual predictors of neonatal hypoglycemia. The proposed statistical analysis is appropriate because of 1) the nested structure of the data and 2) unlike ordinary least squares models, hierarchical models enable us to investigate and explain the sources of both the within and between variations of higher-level factors. Random-intercept models were applied to identify key factors that can independently predict neonatal hypoglycemia among diabetic and non-diabetic mothers. A p value < 0.05 was considered statistically significant for all tests. SAS® version 9.3 was used for data analysis (Institute Inc., Cary, NC, USA).

Hierarchical Modeling Scheme

Multilevel or hierarchical models have been developed to properly account for the hierarchical nesting of data[126-129]. Such modeling techniques should be used in health services research that use national databases, such as HCUP, where data are typically hierarchical in

nature. Conducting research ignoring the hierarchical structure of the data can lead to erroneous conclusions such as incorrect estimation of variances and the available power to detect covariate effects[130-133], increase Type I error rates[134], underestimate standard errors, and lead to substantive errors in interpreting the results of statistical significance tests.[135] To avoid these potential systematic and analytical errors, the current study followed a step-by-step procedure for building hierarchical models. The fundamental theoretical underpinnings of hierarchical modeling are presented in Appendix B.

Model Building Process

To estimate the most parsimonious models that best fit the data, the following three distinct model building processes were conducted. First, intercept-only model or unconditional model were carried out. The intercept-only model was used to calculate the intra-class correlation coefficient (ICC) which estimates how much variation in neonatal hypoglycemia exists between level-2 unit (i.e. hospitals). Second, level-1 fixed effects were added to a model to assess the relationship between level-1 predictors (i.e. individual level characteristics) and neonatal hypoglycemia. Third, level-2 predictors (contextual characteristics) were added to the final model to evaluate the fixed effects of both individual and contextual characteristics (Table IV.1). Forward selection methods ($P \leq 0.10$) were used to identify variables that were eligible for the multivariate analyses.

To assess the model fit, a likelihood ratio test which examines differences in the -2 log likelihood (-2LL) were conducted. Since all models in the current analysis were nested (i.e., models that have been fit using the same data and where one model is a subset of the other), model fit were assessed by examining the changes in the -2LL between models.

Results

A weighted total of 3,733,760 in-hospital births were included in the 2012 KID's inpatient database (Table IV.2). A total of 67,124 (5%) neonates were hypoglycemic. Among neonates included in the study 51% of the neonates were male, while 52% were White, 14% Black, 20% Hispanic, 13% Other (Asian/Pacific and Native Americans). Among neonates with hypoglycemia 50% were small for gestational age, 15% were large for gestational age, 12% had comorbidities, 40% were premature, 44% were delivered by cesarean section, 30% were born from mothers with diabetes, and 2% of the births were associated with mothers with history of substance/alcohol abuse. Almost all mothers were admitted through non-scheduled admission (99%) and close to 80% of births occurred during weekdays.

The majority of newborns had some form of insurance coverage including 46% with Medicaid, 46% with private insurance, and 7% with other types of coverages (self-pay and no charge) (Table IV.3). The median household income in the zip code of patient's residence were proportionately distributed into 28% ($1-$38,999), 25% ($39,000-$47,999), 25% ($48,000 - $62,999), and 22% ($63,000 and above). The majority of births occurred in urban hospitals (88%), in hospitals with bed size greater than or equal to 400 (36%) between July and September (27%). Furthermore, the majority of hospitals were large (63%), privately owned (72%) and well distributed geographically among the four hospital regions including Northeast (17%), Midwest (21%), South (38%), and West (24%). Fifty-seven percent of neonates with hypoglycemia were born in teaching hospitals. Proportionate percentages of births were also observed in teaching (50%) and non-teaching hospitals (50%).

Table IV.4 reports the results from the random intercept model that shows the bivariate relationship between the specified variables and neonatal hypoglycemia. In this analysis male sex (OR 1.3, 95% CI 1.27-1.31), Black (OR 1.1, 95% CI 1.05-1.11), Hispanic (OR 0.8, 95% CI

0.77-0.81) and Other race (Asian/Pacific and Native Americans, OR 0.8, 95% CI 0.82-0.87), morbidity (OR 2.7, 95% CI 2.57-2.73), small for gestational age (OR 9.6, 95% CI 9.41-9.72), large for gestational age (OR 2.9, 95% CI 2.81-2.95), prematurity (OR 7.0, 95% CI 6.78-7.15), delivery by caesarian section (OR 1.9, 95% CI 1.79-1.85), diabetes status (OR 5.6, 95% CI 5.46-5.65), history of substance/alcohol abuse (OR 1.2, 95% CI 1.08-1.22), scheduled delivery (OR 0.8, 95% CI 0.64-0.92), emergency service use (OR 1.5, 95% CI 1.17-2.00), admission between July and September (OR 1.1, 95% CI 1.03-1.08), admission between October and December (OR 1.1, 95% CI 1.06-1.11), neighborhood income above $63,000 (OR 0.9, 95% CI 0.94 - 0.99), teaching hospitals (OR 1.7, 95% CI 1.58-1.87), medium hospital bed size (OR 1.2, 95% CI 1.04 - 1.29), large hospital bed size (OR 1.4, 95% CI 1.26-1.55), privately owned hospitals (OR 1.1, 95% CI 1.05-1.24), urban hospitals (OR 2.0, 95% CI 1.84-2.24), and Medicaid insurance (OR 1.2, 95% CI 1.01-1.35) were significantly associated with neonatal hypoglycemia.

Using the estimate obtained from the empty model, the intra-class correlation coefficient (ICC) which indicates how much of the total variation in the probability of neonatal hypoglycemia is accounted for by the hospitals was calculated. Hierarchical model assumes that the dichotomous outcome from the hierarchical model comes from an unknown latent continuous variable with a level-1 residual that follows a logistic distribution with a mean of 0 and a variance of 3.29. [136,137] As a result, 3.29 were used as the level-1 variance (V_P) while the hospital variance (V_H =0.8381) were obtained from the model.

$$ICC = V_H / [(V_H+V_P)]*100$$

$$ICC = [0.8381 / (0.8381+3.29)]*100 = 20\%$$

The above calculation indicates that 20% of the variability in the rate of neonatal hypoglycemia is accounted by hospitals, leaving 80% of the variability to be accounted by

patients. The result also indicates that there is a statistically significant amount of variability (V_H=0.8381; Z = 26.74; p <.0001) in the odds of developing hypoglycemia between the hospitals.

The model that was constructed to observe the relationship between individual level predictors and neonatal hypoglycemia (model 2) is presented in Table IV.5. In this multivariate analysis female sex (OR 0.8, 95% CI 0.81-0.85), Hispanic (OR 0.8, 95% CI 0.78-0.83), Other race (Asian/Pacific and Native Americans, OR 0.9, 95% CI 0.84-0.90), morbidity (OR 2.6, 95% CI 2.49-2.66), small for gestational age (OR 3.9, 95% CI 3.82-3.98), large for gestational age (OR 2.8, 95% CI 2.76-2.92), prematurity (OR 1.9, 95% CI 1.87-1.99), delivery by caesarian section (OR 1.4, 95% CI 1.38-1.44), diabetes status (OR 2.0, 95% CI 1.95-2.04), history of substance/alcohol abuse (OR 1.2, 95% CI 1.10-1.25), scheduled delivery (OR 0.8, 95% CI 0.64 - 0.92), and emergency service use (OR 1.4, 95% CI 1.02-1.82) were significantly associated with neonatal hypoglycemia.

The final model that combines both the individual and contextual level predictors is presented in Table IV.6. In this analysis male sex (OR 1.2, 95% CI 1.18-1.23), Hispanic (OR 0.7, 95% CI 0.61-0.80) and Other race (Asian/Pacific and Native Americans, OR 0.8, 95% CI 0.78-0.91), morbidity (OR 5.0, 95% CI 4.63-5.40), small for gestational age (OR 9.7, 95% CI 9.25-10.27), large for gestational age (OR 3.1, 95% CI 2.86-3.34), prematurity (OR 3.8, 95% CI 3.44-4.15), delivery by caesarian section (OR 1.5, 95% CI 1.50-1.59), diabetes status (OR 5.1, 95% CI 4.81-5.41), history of substance/alcohol abuse (OR 2.1, 95% CI 1.92-2.29), weekend admission (OR 1.1, 95% CI 1.03-1.08), emergency service use (OR 1.5, 95% CI 1.10-2.00), teaching hospitals (OR 1.2, 95% CI 1.10-1.34), and urban hospitals (OR 1.4, 95% CI 1.21-1.52) were significantly associated with neonatal hypoglycemia.

The best fitting models were determined by using a likelihood ratio test which examines differences in the -2 log likelihood (-2LL). Accordingly, Model 1 to Model 2 and then Model 2 to Model 3 were compared. The calculations for conducting the test between Model 1 and Model 2 is provided below. The positive value (χ^2_{diff}=291,922.9) obtained from the equation 1 shows that model 2 is a better model than model 1.

$$\chi^2_{diff}=(-2LL_{Model\ 1}) - (-2LL_{Model\ 2}) \text{.....equation 1}$$

$$\chi^2_{diff}= (641,605.2) - (349,682.3)$$

$$\chi^2_{diff}= 291,922.9$$

$$\chi^2_{diff}=(-2LL_{Model\ 2}) - (-2LL_{Model\ 3}) \text{.....equation 2}$$

$$\chi^2_{diff}= (349,682.3) - (52,276.9)$$

$$\chi^2_{diff}= 297,405.4$$

After determining that Model 2 was a better fitting model than Model 1, a comparison between Model 2 and Model 3 was made to examine whether the addition of the contextual level variables improved the final model. The calculation from equation 2 (χ^2_{diff}=297,405.4) also indicates that contextual level variables did improve the final model. This process showed that Model 3, a model containing both the individual and contextual level fixed effects, was the best fitting model.

Discussion

In our analysis of the 2012 HCUP KID database, which included more than 3.7 million patient discharges, indicated a 5% (67,124) prevalence of neonatal hypoglycemia. Among hypoglycemic neonates, we determined that 30% of neonates were born from diabetic mothers compared to 7% born from non-diabetic mothers. We also determined that race, morbidity, small

for gestational age, large for gestational age, prematurity, delivery by caesarian section, diabetes status, history of substance or alcohol abuse, scheduled delivery, emergency service use, urban hospitals, and teaching hospitals were significantly associated with neonatal hypoglycemia. As 20% of the variability in the rate of neonatal hypoglycemia is accounted by the hospitals, our specification of hierarchical modeling was appropriate to account for the variability among hospitals.

In our analysis the most robust association, as evidenced by the statistical significance in the multivariate analysis, was found between the individual level characteristics and neonatal hypoglycemia. Our main hypothesis was confirmed by the strong association found between neonatal hypoglycemia and diabetic mothers. Statistically significant associations were found both in the bivariate random intercept model (OR 5.6) and multivariate model (OR 5.1). Most studies of neonatal hypoglycemia not only focused on clinical risk factors but also used small databases from single medical facilities without having proper comparison groups. Our study is unique in that we used a large nationally validated database to determine the individual and contextual risk factors of neonatal hypoglycemia both in diabetic and non-diabetic mothers. The results of the current study highlight the high increased risk (5 fold) of neonatal hypoglycemia among diabetic mothers compared to non-diabetic mothers at the national level. As neonatal hypoglycemia is associated with acute and potentially permanent neurological damage[4,138], hospitals across the United States should develop a more effective method and devise management strategies to identify fetuses from diabetic mothers so that intervention during the neonatal period can be made.

Pertaining to the association between the other individual level risk factors and neonatal hypoglycemia, our results were consistent with data from the literature. For example, Bollepalli

et al.[10] found that large for gestational age or macrosomic infants had 3.5 fold higher odds of developing hypoglycemia compared to non-macrosomic infants. Higher frequencies of maternal diabetes and large for gestational age infants were also observed by Flores-le Roux *et al.*[13] and VanHaltren *et al.*[34] Similar to our findings, Ramos *et al.*[23] indicated that hypoglycemia was statistically associated with prematurity, macrosomia, and Ponderal index, a measure of fetal adiposity. Furthermore, similar to the current analysis, Tundidor *et al.*[101] found that male sex as an independent predictor of neonatal hypoglycemia (OR 2.13). Female newborns are more insulin resistant than boys[156], and this might suggest that male infants might be more prone to neonatal hypoglycemia. Das *et al.*[70] and Ecker *et al.*[155] also found a higher percentage of caesarian section among infants of diabetic mother compared to infants of non-diabetic mothers which is in agreement with our findings. It is also worth noting that infants born from mothers with a history of substance/alcohol abuse were prone to hypoglycemia (OR 2.1).

The Hispanic health paradox was also observed in our study. The paradox states that, despite lower socioeconomic status Hispanics have comparable or better health outcomes than whites. [139,140] Similar to what the paradox states, we found that Hispanic neonates were 30% less likely to develop neonatal hypoglycemia compared to whites (Table IV.6). Lower birth trauma, protective dietary practices, better breastfeeding habits, and strong social networks and support are thought to be the main factors explaining these paradoxical result.[141] Overall, the findings related to the individual risk factors examined by the current study were consistent with the literature.

This is the first study to incorporate contextual characteristics in determining risk factors for neonatal hypoglycemia. Significant associations were observed in the relationship between the contextual variables and neonatal hypoglycemia. In the bivariate random intercept models,

neighborhood income above $63,000 (OR 0.9), teaching hospitals (OR 1.7), large hospital bed size (OR 1.4), privately owned hospitals (OR 1.1), urban hospitals (OR 2.0), and Medicaid insurance (OR 1.2) were significantly associated with neonatal hypoglycemia. In the multivariate analysis, however, only urban (OR 1.4) and teaching hospitals (OR 1.2) were significantly associated with neonatal hypoglycemia.

Among the contextual characteristics, therefore, only urban and teaching hospitals had a significant association with neonatal hypoglycemia. Although no studies were conducted to determine the association of hospital characteristics and neonatal hypoglycemia, our findings were consistent with studies that compared other health outcomes in teaching versus non-teaching and urban versus rural hospitals. The apparent differences in neonatal health outcome in these hospitals could be explained by 1) the quality of care that the hospitals provide and 2) the overall health status of mothers who choose to get services in these hospitals.

The poorer neonatal health outcome in urban hospitals may be due to significant variations in organizational and service mix characteristics that urban and rural hospitals have.[142,143] The literature on health care outcomes in urban versus rural hospitals shows that urban hospitals have higher rates of caesarian section, lower patient safety outcomes, higher adverse event rates, higher rates of infection due to medical care, lower quality of care, and higher rates of pregnancy complication.[144,145] Higher rate of insurance coverage in rural area and younger age of rural mothers could also be the reason for the relatively better neonatal outcomes in rural hospitals.[145,146] In order to balance neonatal outcomes between urban and rural hospitals, targeted intervention efforts that incorporate the particular healthcare needs of rural communities should be introduced across hospitals in the United States.

Regarding neonatal outcomes in teaching hospitals, our findings were also consistent with data from the literature. Differences in neonatal health outcome in these hospitals could also be caused by the quality of care or the overall health status of mothers who received care in these hospitals. Sloan *et al.*[147] found that teaching hospitals had higher postoperative complications in four of six surgical procedures considered in the study. In a study that included 16.9 million Medicare patients, Yuan *et al.*[148] found that teaching hospitals had the highest mortality rates. In a study that included hospitals of Veterans Affairs, Khuri *et al.*[149] also found that complication rate was higher in teaching hospitals in six of seven specialties and four of eight operations.

In the current study, one can also presume that the difference in neonatal health outcomes between teaching and non-teaching hospitals may be attributable to differences in the processes of care. Teaching hospitals, for example, have a more complex structure involving multiple levels of providers including medical students, interns, residents, and fellows, they serve as referral centers for complex services and procedures, and most of them provide care for urban underserved populations.[150, 151] Furthermore, since residents are the primary care provider in teaching hospitals[149,152], there is a possibity that hypoglycemic neonates might be overlooked during delivery.

Improving the quality care during pregnancies is crucial to prevent neonatal hypoglycemia. For example, maternal blood glucose level in labor is independently associated with neonatal hypoglycemia.[100] Providing standardized management for diabetic women in labor using an intravenous insulin-glucose protocol is effective in achieving stable maternal blood glucose levels[99] and reduce neonatal hypoglycemia. With the ongoing emphasis on quality of care, the role of urban and teaching hospitals needs to be carefully scrutinized with regard to

neonatal health outcomes. Efforts should be made to examine further the structures and processes of neonatal care prevailing in teaching and urban hospitals.

The current study was unique in several ways. First, the study used a nationally validated database to assess risk factors of neonatal hypoglycemia. A large national database containing millions of patient-level records has not been utilized in determining predictors of healthcare outcomes related to neonatal hypoglycemia. As a result, the focus of previous research in this area has been limited to assessing clinical risk factors using data generated from individual hospitals. Second, due to the availability of a large database, we were able to include individual and contextual characteristics in our analysis that were not considered in the past. Third, by applying hierarchical models and taking complex survey design into consideration, we were able to investigate and explain the sources of both within-hospital and between-hospital variations. Although the use of hierarchical models is increasing, most studies using clustered data in the health services literature have used ordinary least squares models (OLS). The use of OLS models in clustered data tends to underestimate standard errors for the regression coefficient, resulting in inflated type I error rates and misleadingly tight confidence intervals.[153] By specifying the appropriate hierarchical models, the current study ensured better inferences and yielded more information than results that would have been obtained from traditional standard regression models.

We also identified the limitations associated with the study. First, because of the structure of the KID, we were not able to track patients over time to determine long term health impact of neonatal hypoglycemia on, for example, neurological and cognitive developments. Therefore, interpretation of the results should consider the retrospective cross-sectional nature of the study design. Second, our analyses were limited to the variables that were provided by the data.

Although the variables included in the study are sufficient to understand the overall risk factors of neonatal hypoglycemia, variables such as maternal age, educational background, and individual income could have provided more insightful results. HCUP should consider these variables in future preparations of the KID inpatient databases. Third, only 44 states participate in the HCUP. Furthermore, as the data include only community, non-rehabilitation hospitals, other types of hospitals such as Veterans' Administration and Indian Health System facilities were not included in the data. Our findings may have been underestimated by the exclusion of states and hospitals. Finally, we recognize that errors in providers' understanding of diagnostic coding/groupings may lead to misclassifications of cases. Despite these limitations, however, the KID database is the only nationally validated database that is available to conduct outcomes research on the pediatric population and the use of such validated databases should be encouraged in other areas of health services research.

Conclusions and Recommendations

The purpose of the current study was to construct multilevel models that include individual-level and contextual-level characteristics in order to identify risk factors of neonatal hypoglycemia in diabetic and non-diabetic mothers. We found that infant of diabetic mothers has more than 5-fold increased risk of developing neonatal hypoglycemia compared to infants of non-diabetic mothers. In addition, the increased risk of neonatal hypoglycemia in male, premature, small for gestational age, large for gestational age, and neonates born from mothers with a history of substance or alcohol abuse were also the most relevant results associated with the individual risk factors. Increased awareness of neonatal hypoglycemia in these subgroups should be encouraged to improve and changes clinical practices across hospitals in the United States. Furthermore, we found that infants born in urban and teaching hospitals also had

significantly higher chance of developing neonatal hypoglycemia. Future research should focus on the long term clinical significance of neonatal hypoglycemia by including a broader individual and environmental factors.

Neonatal hypoglycemia is a highly preventable medical condition and yet it poses a significant health threat to the newborns including long-term neurological damage resulting in mental retardation, developmental delay, and personality disorders.[39,49,154] In order to prevent and improve the clinical practices of hypoglycemia the following recommendations, based on the findings from the current study, are forwarded:

1. We found that the individual level risk factors have the most robust association with neonatal hypoglycemia. Therefore, triage treatment system can be developed based on whether the neonate has the specified individual level risk factors. For example, as infants of diabetic mothers have more than 5-fold increased risk of developing hypoglycemia, priority should be given to all diabetic mothers in order to facilitate early diagnosis and treatment of hypoglycemia. Special attention should also be given to infants that are male, premature, small for gestational age, large for gestations age, infants with comorbidities, infants delivered by caesarian section and those born from mothers with a history of substance abuse.
2. Treatment of neonatal hypoglycemia oftentimes involves admission to Neonatal Intensive Care for intravenous dextrose which is costly and disruptive for the establishment of breast feeding.[157] As evidenced by the current study, most of the risk factors can be prevented by establishing a well thought-out parental care in hospitals across the United States so that high risk pregnancies can be identified and closely monitored.

3. In order to balance neonatal outcomes between urban and rural hospitals, targeted intervention efforts that incorporates the particular needs of these hospitals should be introduced. Furthermore, with the ongoing emphasis on quality of care, the role of teaching and urban hospitals needs to be carefully scrutinized with regard to neonatal health outcomes. Efforts should also be made to examine further the structures and processes of neonatal care prevailing in teaching and urban hospitals.

Table IV.1. Model Building Process for Hierarchical Logistic Regression

Models	Variables	Expected Output
Model-1	Empty model, no predictors, only random effect for the intercept	Output used to calculate ICC which provides information on how much variation in neonatal hypoglycemia exists between level-2 units
Model-2	Model 1 + fixed effect for individual level variables	Output indicate the relationship between individual level predictors and neonatal hypoglycemia
Model-3	Model 2 + fixed effect for contextual level variables	Contextual level fixed effect results indicate the relationship between contextual level predictors and the neonatal hypoglycemia. Model 3 also include results from model 2

Table IV.2. Individual Level Characteristics of Neonates with Hypoglycemia

Variables	Hypoglycemic	Non-Hypoglycemic	Total	P Value
Unweighted sample n	51,880	1,055,693	1,107,573	
Weighted population size n	67,124	3,666,636	3,733,760	
Gender n, (%)				
Male	38,495 (57.38)	1,868,004 (50.97)	1,906,499 (51.09)	<.0001
Female	28,598 (43.62)	1,796,628 (49.03)	1,825,227 (48.91)	
Race n, (%)				
White	33,575 (55.35)	1,757,304 (52.34)	1,790,879 (52.39)	<.0001
Black	10,129 (16.70)	479,259 (14.27)	489,388 (14.32)	
Hispanic	9,459 (15.59)	675,793 (20.13)	685,252 (20.05)	
Other[$]	7,493 (12.35)	445,429 (13.27)	452,922 (13.25)	
SGA n, %				
SGA[£]	33,808 (50.37)	348,156 (0.09)	381,964 (10.23)	<.0001
Non-SGA	33,316 (49.63)	3,318,480 (99.91)	3,351,796 (89.77)	
LGA n, (%)				
LGA[¥]	9,723 (14.49)	204,808 (6.00)	214,532 (5.75)	<.0001
Non- LGA	57,401 (85.51)	3,461,828 (94.00)	3,519,228 (94.25)	
Morbidity n, (%)				
With Comorbidities	7,902 (11.77)	64,541 (1.76)	72,443 (7.97)	<.0001
Without Comorbidities	59,222 (88.23)	3,602,094 (98.24)	3,661,316 (92.03)	
Mortality n, (%)				
Died	515 (0.77)	10,408 (0.28)	10,923 (0.29)	<.0001
Alive	66,599 (99.23)	3,656,010 (99.72)	3,722,609 (99.71)	
Prematurity n, (%)				
Premature	27,064 (40.32)	270,550 (7.38)	297,614 (7.97)	<.0001
Non-Premature	40,060 (59.68)	3,396,086 (92.62)	3,436,146 (92.03)	

HCUP KID, Kid's Inpatient Database 2012. All analyses were weighted to account for the complex probability sampling of the dataset. [$]Other Race, Asian/Pacific Islander; Native American; unspecified; [£]SGA, small for gestational age; [¥]LGA, large for gestational age

Table IV.2. Continued.

Variables	Hypoglycemic	Non-Hypoglycemic	Total	P Value
Unweighted sample n	51,880	1,055,693	1,107,573	
Weighted population size n	67,124	3,666,636	3,733,760	
Delivery Mode n, (%)				
Cesarean Section	29,903 (44.55)	114,2704 (31.16)	117,2607 (31.41)	<.0001
Normal Delivery	37,221 (55.45)	2,523,931 (68.84)	2,561,152 (68.59)	
Mothers' Diabetic Status n, (%)				
Diabetic	20,674 (30.80)	259,243 (7.07)	279,917 (7.50)	<.0001
Non-Diabetic	46,450 (69.20)	3,407,393 (92.93)	3,453,843 (92.50)	
Admission Day n, (%)				
Weekday	53,029 (79.00)	2,929,102 (79.89)	2,982,131 (79.87)	<.0001
Weekend	14,095 (21.00)	737,532 (20.11)	751,627 (20.13)	
Scheduled Admission Status n, %				
Scheduled Delivery	164 (0.24)	8,391 (0.23)	8,555 (0.23)	<.0001
Non Scheduled Delivery	6,6874 (99.76)	3,654,687 (99.77)	3,721,561 (99.77)	
Emergency* Dept. Service n, (%)				
Serviced	88 (0.001)	2,214 (0.001)	2,302 (0.06)	<.0001
Not Serviced	67,037 (99.9)	3,664,422 (99.9)	3,731,459 (99.94)	
History of Sub/alc. Abuse n, (%)				
Indicated	1,566 (2.33)	27,584 (0.75)	29,150 (0.78)	<.0001
Not-Indicated	65,558 (97.67)	3,639,052 (99.25)	3,704,610 (99.22)	

*HCUP KID, Kid's Inpatient Database 2012. All analyses were weighted to account for the complex probability sampling of the dataset. *Emergency=HCUP Emergency Department service indicator*

Table IV.3. Contextual Level Characteristics of Neonates with Hypoglycemia

Variables	Hypoglycemic	Non-Hypoglycemic	Total	P Value
Unweighted sample n	51,880	1,055,693	1,107,573	
Weighted population size n	67,124	3,666,636	3,733,760	
Type of Insurance				
Medicaid	30,843 (46.04)	1,695,905 (46.38)	1,726,748 (46.37)	<.0001
Medicare	276 (0.41)	12,991 (0.36)	1,326,7 (0.36)	
Private insurance	31,799 (47.46)	1,687,688 (46.15)	1,719,487 (46.18)	
Other [%]	4,081 (6.09)	259,998 (7.1)	264,079 (7.09)	
Teaching status n, (%)				
Teaching	38,050 (56.69)	1,813,077 (49.6)	1,851,127 (49.58)	<.0001
Non-Teaching	29,074 (43.31)	1,853,559 (50.55)	1,882,633 (50.42)	
Bed Size n, (%)				
Small (1-99)	6,187 (9.22)	406,305 (11.08)	412,492 (11.05)	<.0001
Medium (100-399)	16,811 (25.04)	935,351 (25.51)	952,162 (25.50)	
Large (≥ 400)	44,126 (65.74)	2,324,980 (63.41)	2,369,106 (63.45)	
Ownership n, (%)				
Private	49,286 (73.43)	2,651,655 (72.32)	2,700,941 (72.34)	<.0001
Public	17,838(26.57)	1,014,981 (27.68)	1,032,819 (27.66)	
Neighborhood Income[#]				
1st Quartile (1 - 38,999)	18,405 (27.92)	1,023,540 (28.41)	1,041,945 (28.40)	<.0001
2nd Quartile (39,000 - 47,999)	15,945 (24.19)	886,723 (24.61)	902,668 (24.61)	
3rd Quartile (48,000 - 62,999)	16,086 (24.40)	886,738 (24.61)	902,824 (24.61)	
4th Quartile (63,000+)	15,489 (23.49)	805,520 (22.36)	821,009 (22.38)	

HCUP KID, Kid's Inpatient Database 2012. All analyses were weighted to account for the complex probability sampling of the dataset. [%]Other Insurance = Self-pay, No charge, Other; [#]Income =Median Household Income for patient's Zip code divided into 4 quartiles

Table IV.3. Continued.

Variables	Hypoglycemic	Non-Hypoglycemic	Total	P Value
Unweighted sample n	51,880	1,055,693	1,107,573	
Weighted population size n	67,124	3,666,636	3,733,760	
Admission Season				
January-March	15,388 (22.93)	880,221 (24.01)	895,609 (23.99)	<.0001
April-June	16,034 (23.89)	889,119 (24.25)	905,153 (24.25)	
July-September	18,080 (26.94)	975,669 (26.61)	993,749 (26.62)	
October-December	17,605 (26.23)	920,905 (25.12)	938,510 (25.14)	
Hospital Location				
Rural	5,576 (8.31)	441,988 (12.05)	447,564 (11.99)	<.0001
Urban	61,548 (91.69)	3,224,647 (87.95)	3,286,195 (88.01)	
Hospital Region				
Northeast	11,645 (17.35)	603,344 (16.45)	614,988 (16.47)	<.0001
Midwest	14,847 (22.12)	779,609 (21.26)	794,456 (21.28)	
South	25,813 (38.46)	1,395,779 (38.07)	1,421,592 (38.07)	
West	14,820 (22.08)	887,905 (24.22)	902,725 (24.18)	

HCUP KID, Kid's Inpatient Database 2012. All analyses were weighted to account for the complex probability sampling of the dataset.

Table IV.4. Odds Ratio, 95% CIs, and P Values from Bivariate Random Intercept Models for Individual Level and Contextual Level Risk Factors

Variables	OR[*]	95% CI	P value
Male	1.3	1.273 - 1.313	<.0001
Black	1.1	1.052 - 1.107	<.0001
Hispanic	0.8	0.769 - 0.812	0.0002
Other[$]	0.8	0.820 - 0.869	<.0001
Morbidity	2.7	2.573 - 2.734	<.0001
SGA[£]	9.6	9.409 - 9.718	<.0001
LGA[¥]	2.9	2.812 - 2.945	<.0001
Premature	7.0	6.782 - 7.150	<.0001
Cesarean Section	1.9	1.795 - 1.852	<.0001
Diabetic	5.6	5.455 - 5.648	<.0001
Substance	3.2	2.971 - 3.343	<.0001
Scheduled Delivery	0.8	0.635 - 0.920	0.0046
Weekend	1.0	1.022 - 1.062	<.0001
Emergency[#]	2.2	1.646 - 2.833	0.0018
2nd Quartile (39,000 - 47,999)	0.9	0.970 - 1.017	0.0833
3rd Quartile (48,000 - 62,999)	0.9	0.931 - 0.978	0.1898
4th Quartile (63,000+)	0.9	0.944 - 0.997	0.0302
Lower Income	1.0	1.018 - 1.058	0.0001
Midwest[€]	1.2	1.123 - 1.190	<.0001
South	1.1	1.111 - 1.172	<.0001
West	1.1	1.081 - 1.135	<.0001
2nd Quarter Admission	1.0	0.999 - 1.045	<.0001
3rd Quarter Admission	1.1	1.033 - 1.079	0.0291
4th Quarter Admission	1.1	1.057 - 1.105	<.0001
Teaching Status	1.7	1.579 - 1.865	<.0001
Medium Bed Size (100-399)[Ω]	1.2	1.035 - 1.290	<.0001
Large Bed Size (≥ 400)	1.4	1.263 - 1.549	<.0001
Privately Owned	1.1	1.053 - 1.244	0.0016
Urban Hospitals	2.0	1.838 - 2.242	<.0001
Medicaid[∞]	1.2	1.008 - 1.352	0.0389
Private insurance	1.0	1.017 - 1.056	0.0002
Other[%]	0.9	0.830 - 0.898	<.0001

[*]OR, unadjusted odds ratio; [$]Other Race, Asian/Pacific Islander; Native American; Unspecified; [£]SGA, small for gestational age; [¥]LGA, large for gestational age; CI, confidence interval; [#]Emergency, HCUP Emergency Department service indicator; [€]Northeast region used as reference; [Ω] Small (1-99) used as reference; [∞]Medicare used as reference; [%]Other Insurance, Self-pay, No charge

Table IV.5. Odds Ratio, 95% CIs, and P Values from Model 2 that Indicate the Relationship between Individual Level Predictors and Neonatal Hypoglycemia

Variables	OR[*]	95% CI	P value
Female	0.8	0.81 - 0.85	<.0001
Black	1.0	0.94 - 1.09	<.0001
Hispanic	0.8	0.78 - 0.83	0.0003
Other[$]	0.9	0.84 - 0.90	<.0001
Morbidity	2.6	2.49 - 2.66	<.0001
SGA[£]	3.9	3.82 - 3.98	<.0001
LGA[¥]	2.8	2.76 - 2.92	<.0001
Premature	1.9	1.87 - 1.99	<.0001
Cesarean Section	1.4	1.38 - 1.44	<.0001
Diabetic	2.0	1.95 - 2.04	<.0001
Substance	1.2	1.10 - 1.25	<.0001
Scheduled Delivery	0.8	0.66 - 0.99	0.0473
Weekend	1.0	1.01 - 1.06	0.0075
Emergency[#]	1.4	1.02 - 1.82	0.0370

[+]NH, Neonatal hypoglycemia;[*]OR, adjusted odds ratio; [$]Other Race, Asian/Pacific Islander; Native American; [£]SGA, small for gestational age; [¥]LGA, large for gestational age; CI, confidence interval; [#]Emergency, HCUP Emergency Department service indicator

Table IV.6. Odds Ratio, 95% CIs, and P Values from Model 3 that Indicate the Relationship Between Individual and Contextual Level Predictors and Neonatal Hypoglycemia

Variables	OR[*]	95% CI	P value
Male	1.2	1.18 - 1.23	<.0001
Black	1.0	0.90 - 1.06	0.5739
Hispanic	0.7	0.61 - 0.80	<.0001
Other[$]	0.8	0.78 - 0.91	<.0001
Morbidity	5.0	4.63 - 5.40	<.0001
SGA[£]	9.7	9.25 - 10.27	<.0001
LGA[¥]	3.1	2.86 - 3.34	<.0001
Premature	3.8	3.44 - 4.15	<.0001
Cesarean Section	1.5	1.50 - 1.59	<.0001
Diabetic	5.1	4.81 - 5.41	<.0001
Substance	2.1	1.92 - 2.29	<.0001
Scheduled Delivery	1.0	0.79 - 1.57	0.5470
Weekend	1.1	1.03 - 1.08	<.0001
Emergency[#]	1.5	1.10 - 2.00	0.0106
2nd Quartile (39,000 - 47,999)	1.0	0.94 - 1.05	0.7809
3rd Quartile (48,000 - 62,999)	0.9	0.90 - 1.04	0.4293
4th Quartile (63,000+)	1.0	0.93 - 1.10	0.8046
Midwest[€]	0.9	0.85 - 1.10	0.8046
South	0.9	0.87 - 1.10	0.4293
West	0.9	0.87 - 1.09	0.7809
2nd Quarter Admission	1.0	1.00 - 1.06	0.0002
3rd Quarter Admission	1.1	1.02 - 1.13	0.0040
4th Quarter Admission	1.1	1.05 - 1.15	0.0747
Teaching Status	1.2	1.10 - 1.34	0.0001
Medium Bed Size (100-399)[Ω]	1.1	0.92 - 1.24	0.2939
Large Bed Size (≥ 400)	1.1	0.94 - 1.23	0.4090
Privately Owned	1.0	0.90 - 1.14	0.8254
Urban Hospitals	1.4	1.21 - 1.52	<.0001
Medicaid[∞]	0.9	0.67 - 1.09	0.2124
Private insurance	0.9	0.68 - 1.13	0.3010
Other[%]	0.8	0.60 - 1.04	0.2124

[+]NH, Neonatal hypoglycemia;[*]OR, unadjusted odds ratio; [$]Other Race, Asian/Pacific Islander; Native American; [£]SGA, small for gestational age; [¥]LGA, large for gestational age; CI, confidence interval; [#]Emergency, HCUP Emergency Department service indicator; [€]Northeast region used as reference; [Ω]Small (1-99) used as reference; [∞]Medicare used as reference; [%]Other Insurance = Self-pay, No charge

CHAPTER V

CONCLUSIONS

The overall purpose of this dissertation was to gain a better understanding of the healthcare outcomes and resources utilizations related to neonates with hypoglycemia. To achieve this overarching goal, a series of interrelated studies with multiple sub-goals were carried out. The first goal of this dissertation was to conduct a systematic review in order to investigate whether previous studies only focused on clinical risk factors or included a broader health service-related contextual risk factors in assessing the determinants of neonatal hypoglycemia. The second purpose was to identify the key factors associated with increased hospital cost related to neonatal hypoglycemia in the United States. Lastly, the final purpose of the dissertation was to construct multi-level models that include individual-level and contextual-level characteristics in order to predict neonatal hypoglycemia in diabetic and non-diabetic mothers. In order to summarize the findings within this dissertation the hypotheses from the Chapter I are revisited:

Aim 1 - Hypothesis: In the literature, all studies will focus on the individual level characteristics as determining risk factors for neonatal hypoglycemia.

Findings: The hypothesis related to the first aim was confirmed as the evidence demonstrated that the studies included in the systematic review mainly focused on the clinical risk factors of neonatal hypoglycemia. Although infant-related and mother-related risk factors were specified in these studies broader health service-related contextual risk factors were not included.

Aim 2 - Hypothesis 2.1: Healthcare outcome measures including length of stay, comorbidities, mortality, prematurity, number of procedures, hospital bed size, chronic conditions, and hospital teaching status will predict increased hospital cost associated with neonatal hypoglycemia.

Findings: This hypothesis was supported by the evidence that the indicated healthcare outcome measures were significantly associated with increased hospital cost. To maximize the accuracy of the cost estimation and model prediction, our study, for the first time, used actual cost by converting the total hospital charge to total hospital cost using the cost to charge ratio provided by the HCUP KID database.

Aim 2 - Hypothesis 2.2: Neonates with hypoglycemia will consume a higher percentage of resources associated with hospital births while accounting for a smaller percentage of hospitalization.

Findings: This hypothesis was supported by the evidence that neonates with hypoglycemia consumed 11% of resources associated with hospital births while accounting for only 1.5% of hospitalization. Although healthcare resource utilization of hypoglycemia has been adequately addressed in the adult population, this topic has not been studied in neonates with hypoglycemia. As a result, these findings will provide important information to help allocate resources efficiently.

Aim 3 – Hypothesis 3.1: Infants born from diabetic mothers have significantly higher chance of developing hypoglycemia compared to those born from non-diabetic mothers.

Findings: This hypothesis was confirmed by the strong association found between neonatal hypoglycemia and diabetic mothers. Statistically significant associations were observed both in the bivariate random intercept model (OR 5.6) and multivariate model (OR 5.1).

Aim 3 – Hypothesis 3.2: The addition of the contextual factors will enhance the predictive power of the model that will be constructed to predict neonatal hypoglycemia in diabetic and non-diabetic pregnancies.

Findings: This hypothesis was confirmed by the findings of the investigation. The calculations form the -2 log likelihood ratio test indicated that the addition of the contextual variables improved the final predictive model. In addition, the magnitudes of the odds ratios on many of the variables in model 2 has also shown a significant increase in model 3. This magnifies the importance of using border environmental risk factors in health services research.

Summary and Policy Implications

The systematic review included in this dissertation (Project I) provided an important synthesis of the available data on current neonatal hypoglycemia literature. Project I determined that there is evidence supporting the clinical importance of giving attention to infants of diabetic mothers. However, the systematic review also determined that previous neonatal hypoglycemia studies had been solely focused on clinical or individual level risk factors. The infant-related clinical risk factors identified in Project I were small for gestational age, large for gestational age, macrosomia, prematurity, lower cord blood glucose, Ponderal Index, and male sex. In addition, ethnic origin, diabetes diagnosed prior to 28 weeks of gestation, pre-pregnancy BMI $\geq$25 kg/m^2, hyperglycemia, blood glucose, maternal diabetes type, and material HbA1c were also identified as mother-related clinical risk factors. As such, the project identified the need to include a broader contextual level risk factors in assessing the determinants of neonatal hypoglycemia.

Project II sought to determine the overall hospital cost estimates in neonates with hypoglycemia and to identify predictors of increased hospital cost. Since previous studies have focused on estimations of the economic cost of hypoglycemia in the adult population[44-49], Project II is the first study providing an empirical estimate of the hospital cost of neonatal hypoglycemia at the national level. To maximize the accuracy of the cost estimation and prediction of increased

cost, Project II used cost to charge ratio to covert total charge to total cost. Furthermore, Project II determined that medium and large hospital bed sizes, length of stay, teaching hospitals, composite neonatal comorbidities, prematurity, occurrence of chronic conditions, and mortality as independent predictors of increased hospital cost associated with neonatal hypoglycemia. Lastly, Project II demonstrated that neonates with hypoglycemia consumed 11% of resources associated with hospital births while accounting for only 1.5% of hospitalization. Although Project II encompassed the investigation of the resource utilization, further research is needed to explore longitudinal trends of hospital cost and their variation among different patient and hospital characteristics.

Project III focused on the identification of individual and contextual level risk factors among diabetic and non-diabetic mothers using multilevel modeling scheme. Project III determined that 30% of neonates were born from diabetic mothers compared to 7% born from non-diabetic mothers and that 20% of the variability in the rate of neonatal hypoglycemia is accounted by the hospitals. Furthermore, Project III determined that neonates had more than 5-fold increased risk of developing hypoglycemia. Lastly, project III determined that male sex, Hispanic race, Asian/Pacific and Native Americans race, morbidity, small for gestational age, large for gestational age, prematurity, delivery by caesarian section, history of substance/alcohol abuse, scheduled delivery, emergency service use, urban hospitals, and teaching hospitals as significant predictors neonatal hypoglycemia. In Project III the most robust association was found the between the individual level risk factors and neonatal hypoglycemia. Future research should focus on the long term clinical significance of neonatal hypoglycemia by including a broader individual and environmental factors.

Neonatal hypoglycemia is the most frequently encountered metabolic disorder of newborn infants and has been linked to various adverse health outcomes[4,5] including neurological damage and death.[1,49] The results of the investigations within this dissertation estimated the total hospital cost and identified predictors of increased cost related to neonatal hypoglycemia for the first time. With the current increase in the overall healthcare cost in the United States, there is a strong interest to enhance efficacy through reform and system improvement.[50,158] A better understanding of total cost estimates and factors associated with increased hospital cost is important to help hospitals improve the efficiency of the care they provide and to decrease costs while maintaining high quality of care. Furthermore, the current dissertation identified the key individual and contextual level risk factors that can help neonatal care providers create triage treatment system to identify hypoglycemic neonates more quickly and efficiently. Hospitals across the United States should develop, therefore, a more effective method and devise management strategies to identify fetuses from diabetic mothers so that intervention during the neonatal period can be made. In addition, in the current dissertation urban and teaching hospital were significantly associated with neonatal hypoglycemia. Although one can argue that focusing on the mothers who are coming to these facilities is more important in terms of preventing neonatal hypoglycemia, the quality of services in these facilities could also be a significant factor. As neonates with asymptomatic hypoglycemia could easily be neglected of proper care[16,41,77,121], the quality of neonatal care provided by hospitals is crucial to identify these subgroups. As a result, the processes of care in urban and teaching hospitals should be carefully scrutinized with regard to neonatal health outcomes. Although hypoglycemia is the most common metabolic disorder of the newborn, with proactive prenatal care, proper case management, and appropriate intuitional policy for treatment, it can be prevented almost entirely.

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APPENDICES

Appendix A. Codes for the Identification of Variables

Variables	ICD-9-CM/ PRCCS/ DXCCS/ DRG24
Neonatal Hypoglycemia	775.6 (ICD-9-CM)
Large for Gestational Age	766.1 (ICD-9-CM)
Small for Gestational Age	764.0, V21.30- V21.35 (ICD-9-CM)
Prematurity	386, 387, 388, 375 (DRG24)
History of Alcohol/Substance Abuse	660, 661 (DXCCS); 52,433,521,523 (DRG24)
Complicated Pregnancy	219 (DXCCS)
Delivery by Cesarean Section	669.7; V3001(ICD-9-CM)/ 134, 134,740,741,742,743,744,745,746,747,748,749 (PRCCS)/ 370, 371 (DRG24)
Indicator of Diabetic Status (Type I, Type II, Gestational)	250.01-250.93, 775.0, 648.03, 648.83 (ICD-9-CM)/ 49, 50, 186 (DXCCS)/295 (DRG24)
Comorbidities	
Jitteriness	796.9 (ICD-9-CM)
Hypotonia	781.3 (ICD-9-CM)
Lethargy	780.7 (ICD-9-CM)
Irritability	799.22 (ICD-9-CM)
Apnea	786.03 (ICD-9-CM)
Tachypnea	786.06 (ICD-9-CM)
Poor feeding	783.3 (ICD-9-CM)
Hypothermia	991.6 (ICD-9-CM)
Sepsis	995.91, 771.81 (ICD-9-CM)
Seizures	345.0-345.9 (ICD-9-CM)
Neurodevelopmental Delay	315.0-315.9 (ICD-9-CM)

ICD-9-CM= International classification of diseases, 9th version; PRCCS= Clinical classification software category for all procedures; DRG24= Diagnostic related groups, version 24; DXCCS=Clinical classifications software category for all diagnosis

Appendix B: Single-level versus Multi-level Models

Let us assume that Y is neonatal hypoglycemia with binary outcome which follows the Bernoulli distribution $Y \sim Bin\ (1, \pi)$. Equation 1 indicate a single-level logistic regression where $i = 1 \ldots I_j$ is the individual level variable, $j = 1 \ldots J$ is the contextual level variable, conditional on the risk factor for neonatal hypoglycemia x (e.g. prematurity). Ordinary logistic regression model (equation 1) assumes individual level random errors e_{ij} are independent with moments $E\ (e_{ij}) = 0$ and $Var\ (e_{ij}) = \sigma_e^2 = \pi_{ij}(1 - \pi_{ij})$.[159] Equation 2 indicates the probability function of the outcome variable and it has the ij subscripts to show that that individual level factors are nested within the contextual level factors (i.e. the subjects within hospitals). However, this model is single-level because it does not contain contextual level effects.

To extend the single-level model into multi-level analysis, we add design level variables to equation 1 so that each higher-level unit has its own intercept in the model (equation 3).[160-162] In this case, the hospital intercept is treated as random effect $\alpha_j\ (j = 1 \ldots J)$. This leads to a random intercept model (equation 4) which is the combination of a grand mean (α) and a deviation from that mean (u_j). The random variable u_j is assumed to be normally distributed $u_j \sim N\ (0, \sigma_u^2)$ and independent of the single level random error e_{ij}.

The model in equation 4 is a multi-level logistic regression model with two levels of hierarchy. At level 1, outcome is expressed as the sum of an intercept for the patient's hospital and the patient's risk factor. At level 2, the hospital level intercepts as the sum of an overall mean and the random deviations from that mean are specified. Equation 5 is a hierarchical/mixed model because it has both fixed effects (α, β) and random effects(u_j). However, equation 5 has treat the hospital effect as a random effects only and does not include hospital level predictors (level-2).

Single-Level Logistic Regression Model

$$Y_{ij} = \pi_{ij} + e_{ij}, \quad \text{Eq.1}$$

$$\text{logit}(\pi_{ij}) = \log(\frac{\pi_{ij}}{1-\pi_{ij}}) = \alpha + \beta x_{ij}$$

$$\pi_{ij} = \frac{\exp(\alpha + \beta x_{ij})}{1 + \exp(\alpha + \beta x_{ij})} \quad \text{Eq.2}$$

Random Intercept and Level-1 Fixed Effects

$$\text{logit}(\pi_{ij}) = \alpha_j + \beta x_{ij} \quad \text{Eq.3}$$

$$\text{logit}(\pi_{ij}) = \alpha_j + \beta x_{ij}$$

$$\alpha_j = \alpha + u_j \quad \text{Eq.4}$$

$$\text{logit}(\pi_{ij}) = \alpha + u_j + \beta x_{ij} \quad \text{Eq.5}$$

Random Intercept and Level-1 + Level-2 Fixed Effects

$$\text{logit}(\pi_{ij}) = \alpha_j + \beta x_{ij} \quad \text{Eq.6}$$

$$\alpha_j = \alpha + \gamma z_j + u_j$$

$$\text{logit}(\pi_{ij}) = \alpha + \gamma z_j + u_j + \beta x_{ij} \quad \text{Eq.7}$$

As the objective of the current study is to also see the effects of contextual level attributes, a hospital level predictors (e.g. *z* for teaching status) should be included in equation 4. Equation 6 now indicates that the intercept α_j is a linear combination of a grand mean (α), hospital fixed effect (γ), and hospital foxed effect (u_j). Equation 7 is the final mathematical model that contain the individual level and hospital level fixed effects. For the purpose of simplicity, during the model building process, only one individual and one hospital level variables were included. However, in the actual analysis multiple individual and hospital or contextual level variables were included.

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