HEALTH SERVICE UTILIZATION OF LATE PRETERM INFANTS

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By

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ABSTRACT

Preterm birth (< 37 weeks gestation) is a major health burden for affected children. Although the risk of health problems increases as the gestational age decreases, research in the last decades has revealed that even late preterm infants born at 34-36 weeks gestational age have higher mortality and morbidity than term infants. Because late preterm infants constitute three fourths of preterm infants, they are important from both public health and health policy perspectives. This doctoral thesis sought to answer important knowledge gaps in health service utilization of late preterm infants via three studies.

Study A, a systematic review and meta-analysis comparing health service utilizations of late preterm infants with those of term infants, found that late preterm infants had increased hospitalization compared with term infants that persisted from the neonatal period through adolescence. Study B is a cohort study evaluating the re-admissions and emergency department visits by late preterm and term singletons and twins for the first 5 years after birth. Study B demonstrated that late preterm infants had higher re-admission rates than term infants although differences in twins were less pronounced than in singletons. Study C is a

population-based cohort study with cost analyses assessing the health care costs and resource utilization related to three different discharge timings of late preterm and term singletons: early (< 48 hours), late (48-71 hours), and very-late (72-95 hours) discharge after birth. Study C found that early discharge was not associated with the reduction of health care cost in late preterm infants, and instead was associated with an increase in the cost in term infants over the first year after birth. These findings are useful for parents, care providers, health policy makers, and guideline developers to provide optimal care for late preterm infants.

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I am extremely grateful to my PhD supervisor, Prof. Sarah D McDonald, for her continuous dedicated support for me throughout my graduate school life. Her kind and encouraging support enabled me to become what I am now today. From her, I have learned numerous things required to be an excellent independent investigator as well as a great human being. I am greatly honored to be a PhD student and learn research under her supervision.

I would like to thank my PhD committee members, Dr. Joseph Beyene and Dr. Daria O'Reilly, for their strong support for me. Their excellent feedback and advice on my thesis studies greatly help me improve the quality of study methods.

Lastly, I would like to dedicate this PhD thesis to my parents, Hiromichi and Miyoko, and my wife, Reina, and my daughter, Yume.

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LIST OF SUPPLEMENT MATERIAL FOR STUDIES A-C

Chapter 2: Study A

LIST OF ABBREVIATIONS

95% CI: 95% confidence interval(s)

AIC: Akaike Information Criterion

aIRR: adjusted incidence rate ratio

aMCD: adjusted mean cost difference

aOR: adjusted odds ratios

CIHI: Canadian Institute for Health Information

CINAHL: Cumulative Index to Nursing and Allied Health Literature

DAD: Discharge Abstract Database

ED visit(s): emergency department visit(s)

GA: gestational age

GLM: generalized linear regression models

HR: hazard ratio

HSU: health service utilization(s)

ICD: International Classification of Diseases

ICES: Institute for Clinical Evaluative Science

IRR: incidence rate ratio

MOMBABY: Mother-Baby Linked Database

NACRS: National Ambulatory Care Reporting System

NICU: neonatal intensive care units

NOS: Newcastle Ottawa Scale

OHIP: Ontario Health Insurance Plan

OR: odds ratio

PhD: Doctor of Philosophy

PTB: Preterm Birth

RR: Relative risk(s)

RSV: respiratory syncytial virus

SDS: Same Day Surgery Database

UK: United Kingdom

USA: United States of America

DECLARATION OF ACADEMIC ACHIEVEMENT

This is a "sandwich" thesis that included three individual studies (A, B, and C) in Chapter 2-4 prepared for submitting to peer review journals. Study A has been provisionally accepted to *Pediatrics*. Study B is submitted to *Pediatrics*. Study C is ready for submission to *JAMA Pediatrics*. I was the first author and corresponding author for all the studies.

For all the studies, under the supervision of Dr. Sarah D McDonald, I developed the study protocols, obtained research ethics board approval, obtained study data, conducted statistical analyses including coding in SAS or R, summarized and interpreted the results, drafted the manuscripts, revised the final manuscript based on feedback from other co-authors, and if applicable, submitted to a peer review journal and responded to reviewer's comments. In addition, for study A, I was the first reviewer, and developed literature search strategies in consultation with a research librarian, Ms. Neera Bhatnagar (McMaster University, Ontario), conducted literature search using OVID, contacted authors of included studies for obtaining additional study data.

For this doctoral thesis, I drafted the INTRODUCTION (Chapter 1) and CONCLUSION (Chapter 5) and revised them based on feedback from my supervisor and PhD committee members.

My PhD supervisor, Dr. Sarah D McDonald, supervised all the process in all three studies and this doctoral thesis (INTRODUCTION and CONCLUSION sections) and provided funding to acquire the study data for study B and C.

My PhD committee members, Dr. Joseph Beyene and Dr. Daria O'Reilly, provided critical advice in all three studies for developing the study protocols, performing the analyses, interpreting the results, and revising the manuscripts as well as reviewing and providing feedback on this doctoral thesis (INTRODUCTION and CONCLUSION sections). In particular, issues related to the statistical analyses in all three studies were handled by myself in consultation with Dr. Joseph Beyene, and the issues related to cost analyses in study C handled by myself in consultation with Dr. Daria O'Reilly.

There are other co-authors or collaborators in this thesis as noted below:

In study A, Dr. Anne-Mary Lewis-Mikhael was a second reviewer for the systematic review, provided feedback on the study protocol, conducted abstract & title screening, conducted full text screening, extracted data, performed risk of bias assessment, and critically reviewed and revised the manuscript.

In study A, Ms Laura Nguyen, Ms Simran Sharma, and Ms Cathy Lu (undergraduate students of the McMaster University) assisted with obtaining full text articles of studies, or formatting the manuscript.

In study B and C, Dr. Shoo Lee and Dr. Prakesh Shah (Professor, University of Toronto) provided advice on study protocols, and critically reviewed and revised the study manuscripts.

In study B, Dr. Astrid Guttmann (Senior core scientist of the Institute for Clinical Evaluative Science) provided advice on the study protocol, and critically reviewed and revised the study manuscript.

In study B and C, Mrs Shudong Li and Saskin Refik (data analysts from ICES Data and Analytic Services) assisted with developing the study protocol and created the data-set for these studies from the ICES databases.

CHAPTER 1: INTRODUCTION

Definition of preterm and late preterm

Preterm births are defined as births before 37 completed weeks gestational age .[1] Births at 37 to 41 weeks gestational age are called term births. The World Health Organization categorizes preterm births into extremely preterm (< 28 weeks gestational age), very preterm (28 to 31 weeks gestational age), and moderate to late preterm (32 to 36 weeks gestational age).[1] To emphasize the health issues of preterm infants close to term, preterm infants born at 34 to 36 weeks gestational age were defined as late preterm infants by the expert panel invited by the National Institute of Child Health and Human Development of the National Institutes of Health in 2005.[2] More recently, even term births have been further categorized into early term (37-38 weeks gestational age) and full term (39-41 weeks gestational age) births.[3]

Text-box 1: Definition of terminology for gestational age (GA) categories or preterm infants

- Extremely preterm < 28 weeks GA
- Very preterm 28-31 weeks GA
- Moderate preterm 32–33 weeks GA
- **Late preterm 34–36 weeks** GA
- **Term 37–41 weeks GA**
  - Early term 37–38 weeks GA
  - Full term 39–41 weeks GA
- Post term ≥42 weeks GA

Epidemiology of preterm and late preterm infants

Worldwide, approximately 14.9 million infants, 11% of all livebirths, were estimated to be born preterm in 2010.[4] The proportion is smaller in high-income and upper-middle income countries (9.3% and 9.4%, respectively) than lower middle-income or low-income (11.8% and 11.3%, respectively).[4] Even among high-income countries, there is a variation in the proportion of preterm infants (e.g. 5.9% in Japan, 5.9% in Sweden, 7.8% in Canada, 7.8% in the United Kingdom [UK], 12.0% in the United State of America [USA]).[4] Furthermore, it was reported that the proportion of preterm births increased from 7.2% in 1990 to 8.6% in 2010 in the "Developed regions" (e.g. Japan, Canada, USA, European countries, Australia, New-Zealand, Russia based on the Millennium Development Goal regional groupings).[4]

Among the gestational age categories of preterm infants in the Text-box 1, the group of late preterm infants is the largest. In Canada with 380,323 live-births in 2013, the proportions of extremely, very, moderate, and late preterm infants were 5.9%, 8.8%, 11.5%, and 73.6%, respectively, among all preterm live-births.[5] A population-based international comparative study reported the proportion of

late preterm infants and its trend between 6 high-income countries in North American and Europe.[6] Late preterm infants among all preterm live-birth singletons were 76.3% in Canada, 74.9% in the USA, 73.6% in Denmark, 75.9% in Finland, 70.9% in Norway, and 74.6% in Sweden in years between 2006 and 2015.[6] The proportions decreased in Norway and USA over the period, but not in other countries.[6]

Mortality of preterm births

Preterm birth is a major health problem among children due to its high morbidity and mortality.[7] Worldwide, 2.7 million newborns < 28 days of age die each year, in whom preterm-related complications are the leading cause of death (35% of newborn deaths).[8] The mortality of preterm infants decreases with advancing gestational age at birth.[9] The Canadian Neonatal Network reported the mortality before discharge among preterm infants who received active care (or resuscitation) at births was 77% at <23 weeks, 25% at 24 weeks, 12% at 26 weeks, 4% at 28 weeks, and 1% at 30 weeks gestational age in Canada in 2015.[10]

Morbidity of extremely or very preterm infants

Surviving preterm infants face higher risks of a wide range of long-term health problems including neurosensory impairment, respiratory problems, and behavioral and psychiatric problems. A population-based cohort study from the United Kingdom (UK) and Ireland reported that 45% of infants born at < 26 weeks gestational age had moderate to severe neurosensory disability including cerebral palsy (9%), cognitive deficit (40%), hearing impairment (2%), and visual impairment (8%) at 11 years of age.[11] The rate of moderate to severe morbidity was 48%, 54%, and 39% for infants at <24, 24, and 25 weeks gestational age, respectively.[11] A Canadian near-population-based cohort study reported that 16.5% of very preterm infant survivors born at < 29 weeks gestational age in 2009-2011 had significant neurodevelopmental impairment at 21 months of corrected age.[12] The rates of the significant neurodevelopmental impairment for infants at <24, 24, 25, 26, 27, and 28 weeks gestational age was 37%, 29%, 21%, 18%, 15%, and 8%, respectively.[12] A systematic review found very preterm or very low birth weight infants (≤ 33 weeks gestational age or ≤ 1500 g birth weight, respectively) had significant lower academic achievement (mathematics, reading, and spelling), behavioral problems (attention and internalizing problems),

and higher-order neurocognitive function (i.e. executive function) deficits.[13] Furthermore, these various medical disabilities and resultant social disabilities were reported to persist in adulthood.[14] In 2005, preterm birth was estimated to cost the USA approximately $ 26.2 billion, which amounts to around $51,600 per preterm birth.[15]

Mortality and morbidity of late preterm infants

While all preterm infants have increased mortality and morbidity, the risk increases as gestational age at birth decreases.[14, 16] Therefore, previous studies have mainly focused on very preterm infants born at <32 weeks gestational age.[17] However, in the last decade, it has been revealed that even late preterm infants have increased mortality[18] and morbidity in both short- and long-term compared with term infants.[14, 18-21] A large population-based cohort study reported that the all-cause mortality of late preterm singleton infants was 9.2 and 13.3 per 1,000 infants in the USA and Canada (except for Ontario), respectively.[22] The mortality was higher than term infants with RR 2.9 [95%CI 2.8, 3.0] and RR 4.5 [4.0, 5.0] in the USA and Canada, respectively.[22] A systematic review reported the increased risk of respiratory distress, intraventricular hemorrhage, and neonatal

deaths in late preterm infants compared with term infants (relative risk, RR 17.3 [95 confidence interval: 95% CI 9.8, 30.6]), RR 4.9 [95% CI 2.1, 11.7], and RR 5.9 [95% CI 5.0, 6.9], respectively) along with the increased risk of cerebral palsy and cognitive deficit (RR 3.1 [95% CI 2.3, 4.2], and RR 1.5 [95% CI 1.2, 1.9], respectively).[23] Lower academic performance and higher special education requirements of late preterm infants compared with term infants were also reported.[24] A Norwegian population-based cohort study reported that adults who were born late preterm were at significantly increased risk for disorders of psychological development, behavior and emotion (RR 1.5 [95% CI 1.2, 1.8]), disabilities affecting working abilities (RR 1.4 [95% CI 1.3, 1.5]), as well as cerebral palsy (RR 2.7 [95% CI 2.2, 2.3]) and cognitive deficit (RR 1.6 [95% CI 1.4, 1.8]).[14] Although these adverse outcomes were less severe in late preterm infants than in younger preterm infants (e.g. very preterm infants), late preterm infants are important from public health or health policy perspectives due to their great number in the population.[25] In Canada, approximately three quarters (74%) of preterm births are late preterm;[26] therefore, the population of late preterm infants has substantial impact on the health care system.[25]

Health Service Utilization

Health service utilization is "the measure of the population's use of the health care services available to them"[27] and includes the use of various health care resources including hospital services, home care services, special care services, and human resources of health care professionals. Health service utilization depends on a population's demand and supply of health care and therefore reflects efficiency and fairness of the health system as well as ease of access to services.[28] A study of health service utilization provides important knowledge which can be used by health policy makers and economists to assess the use of the current health care system and assist in developing future budget.

Administrative database and ICES databases

Healthcare administrative databases are databases that routinely collect data such as discharge abstracts, prescription records, physician claims, for the purpose of administrating health care system.[29] As the advances in information technology made it easier to collect, store, and access large healthcare data, many administrative databases have been used for other than administrative purpose such as for clinical research. There are many healthcare administrative databases in the world.[30-33]

In Canada, all provincial governments fund inpatient and outpatient hospital services and physician services, and some provincial governments also fund other services (e.g. prescription drugs, home care, and long-term care).[34] Therefore, these provincial governments maintain various administrative databases regarding utilization and cost of these health services.[34] The Institute for Clinical Evaluative Science (ICES) databases that I used in this thesis is an organization given authority to link multiple databases in Ontario, using unique encrypted identifiers, including Discharge Abstract Database (DAD, hospitalization database), Mother-Baby Linked Database (MOMBABY), National Ambulatory Care Reporting System (NACRS, emergency department [ED] visits database), Same Day Surgery Database (SDS), Ontario Health Insurance Plan database (OHIP, billing information database), and Registered Persons Database files (RPDB, vital statistics data).[33, 35] Furthermore, at a national level, the Canadian Institute for Health Information (CIHI) has developed and maintained a health information system (CIHI database) that integrated various provincial administrative databases data by developing data standards for databases and collecting provincial databases' data.[34] Some of the ICES databases' data such as

DAD and NACRS are submitted to and included in the CIHI databases. However, we used the provincial-level ICES database rather than the national-level CIHI databases in this thesis because the ICES databases covered broader areas of administrative data such as billing information. In addition, the NACRS database (ED visits data) in CIHI did not cover many ambulatory-care institutions in some provinces unlike the NARCS database in ICES that covered most of institutions in Ontario.[36]

Health Service Utilization of Late Preterm Infants

Although many previous studies reported increased hospital service utilizations of very preterm infants compared with term infants,[37-40] the data for late preterm infants were limited, especially long-term data after the immediate neonatal period (after 28 days of age).[41-44] Given the substantial volume of health service resources and costs are spent on late preterm infants due to their large number in the population, this information gap has been problematic.[17] Furthermore, few studies have examined the impact of interventions such as early discharge after birth hospitalization particularly in late preterm infants, a measure which in term infants was hoped to mitigate health care costs.

The overall goal and three doctoral thesis studies

Hence, the overall goal of this doctoral thesis was to fill important knowledge gaps regarding health service utilization of late preterm infants through the three studies A, B, and C in Chapter 2, 3, and 4, respectively.

Study A (Chapter 2) is a systematic review and meta-analysis comparing the health service utilizations of late preterm infants with those of term infants. Although several previous systematic reviews assessed the mortality and morbidity of late preterm infants along with their long-term health problems, there was no systematic review specifically assessing the health service utilization of late preterm infants after initial discharge from birth hospitalization.[21, 23, 24, 45] Therefore, study A is the first systematic review on the topic, and by summarizing the current evidence on health service utilization of late preterm infants, study A served as a comprehensive backdrop for studies B and C in this thesis.

Study B (Chapter 3) is a cohort study evaluating the hospital service utilizations (e.g. admissions, ED visits) after initial discharge by late preterm and term singletons and twins for the first 5 years after initial birth hospitalizations. Data were collected using a large population-based, administrative database in

Ontario. Study B assessed the issues that overlapped with study A and evaluated areas where the information was found to be limited in study A such as (1) health service use of late preterm twins, (2) ED visits of late preterm infants, and (3) long-term health service utilizations after 1 year of age. The consideration of twins is important in assessing late preterm infants as the proportion of twins is much higher in late preterm infants (15%) than in term infants (1.5%).[46] Therefore, unlike previous studies summarized in study A, study B stratified the analyses by singletons and twins and compared the differences in hospital service use of late preterm infants with that of term infants.

Study C (Chapter 4) is a population-based cohort study with cost analyses assessing the safety and health care costs related to three different discharge timings of late preterm and term singletons: early (< 48 hours), late (48-71 hours), and very-late (72-95 hours) discharge after birth. Although studies A and B highlighted the significant increased health service utilization in late preterm infants compared with term infants for all-causes or various specific causes, they did not evaluated the impact of interventions such as early discharge after birth, a measure which was previously assessed for term infants to mitigate health care

costs.[47] There was not much previous data on the early discharge of late preterm infants. Hence, study C investigated how different discharge timings from initial birth hospitalizations are associated with re-admissions, ED visits, and health care costs of healthy late preterm and term vaginally-born singletons. This allowed me to explore the optimal timing for minimizing the resource use and cost for late preterm and term infants.

CHAPTER 2

STUDY A

HEALTH SERVICES USE BY LATE PRETERM AND TERM INFANTS FROM INFANCY TO ADULTHOOD: A META-ANALYSIS

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Health Services Use by Late Preterm and Term Infants from Infancy to Adulthood: A Meta-Analysis

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The authors have no conflicts of interest relevant to this article to disclose.

Abbreviations:

HR: hazard ratio; HSU: health service utilization(s); IRR: incidence rate ratio; NOS: Newcastle Ottawa Scale; OR: odds ratio; RR: relative risk; RSV: respiratory syncytial virus

Table of Contents Summary: (24/25 words)
A systematic review and meta-analysis summarizing various health service utilization of late preterm infants compared with term infants from the neonatal period to adulthood.

Contributor's Statement:

Dr Isayama conceived the study idea, developed the study protocol, developed literature search strategies, conducted the literature search and review, selected eligible studies, extracted study data, assessed the quality of evidence, conducted the meta-analyses, summarized the study results, and wrote the first draft manuscript.

Dr Lewis-Mikhael provided advice for developing the study protocol, conducted the literature review, selected eligible studies, extracted study data, assessed the quality of evidence, and critically reviewed and revised the manuscript.

Drs O'Reilly and Beyene provided advice for developing the study protocol, conducting meta-analyses, and summarizing the study results, and critically reviewed and revised the manuscript.

Dr McDonald supervised all aspects of this study, conceived the study idea, developed the protocol, provided advice for conducting meta-analyses and summarizing the study results, and critically reviewed and revised the manuscript.

All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work**.**

Abstract

Context: Late-preterm infants born at 34-36 weeks gestation have increased risks of various health problems. Health service utilization (HSU) of late-preterm infants has not been systematically summarized before.

Objective: To summarize the published literature of the short- and long-term HSU after initial discharge home by late-preterm infants versus term infants from infancy to adulthood.

Data Sources: MEDLINE, EMBASE, CINAHL, and PsycINFO.

Study Selection: Cohort and case-control studies that compared HSU (admissions, emergency department visits, etc.) between late-preterm infants and term infants were included.

Data Extraction: Data including study design, setting, population, HSU, covariates, and effect estimates were extracted.

Results: Fifty-two articles were included (50 cohort and 2 case-control studies). Meta-analyses with random effect models using inverse variance method found that late-preterm infants had higher chances of all-cause admissions than term infants in all the time periods. The magnitude of the differences decreased as the age increased from the neonatal period to adolescence with adjusted odds ratios from 2.34 (95% confidence intervals 1.19-4.61) to 1.09 (1.05-1.13) and adjusted incidence rate ratios from 2.62 (2.52-2.72) to 1.14 (1.11-1.18). Late-preterm infants had higher rates of various cause-specific HSU than term infants, for jaundice, infection, respiratory problems, asthma, and neurological /mental health problems in certain periods including adulthood.

Limitations: Considerable heterogeneity existed and was partially explained by the variations in the adjustment for multiple-births and gestational-age ranges of the term infants.

Conclusions: Late-preterm infants had higher risks for all-cause admissions from the neonatal period through adolescence as well as for various cause-specific HSU.

BACKGROUND

Preterm births are one of the leading health burdens on children because of their high mortality and morbidity.[1] Since the risk increases as gestational age at birth decreases, clinicians and researchers tend to pay less attention to late preterm infants born between 34 to 36 completed weeks of gestation than more immature preterm infants.[2] Historically, late preterm infants, previously referred to as near-term infants, were managed similarly to term infants in nurseries after births.[3] However, it was revealed that even late preterm infants had significantly higher mortality and morbidity compared with term infants.[3] Although individual infant's risks are lower than those of more premature infants, the impact on a population level is likely substantial because late preterm infants make up approximately 75% of preterm infants.[4, 5] Furthermore, some potential adverse sequelae of late preterm birth, including cerebral palsy, cognitive problems, psychological or behavioral problems, persist to later in life.[6]

Due to the increased morbidity, late preterm infants use more health services including hospital admissions and emergency department or outpatient visits. Many previous studies on health service use of late preterm infants focused on the neonatal period.[7, 8] However, the information about long-term health service utilization of late preterm infants was scarce, especially after 1 year of age,[8] and the data have never been systematically summarized to date. The aim of this study was to systematically summarize the published literature of the health

service utilization after the initial birth hospitalization of late preterm infants compared with those of term infants, from the neonatal period to adulthood.

METHODS

Literature Search, Screening, and Data Extraction

The literature search was conducted in 4 electronic databases including MEDLINE, EMBASE, CINAHL, and PsycINFO from their inception to September 15, 2016 (Please see eTable 1 in the supplement for the specific search terms and search strategies). This was complemented by hand searching of references of relevant narrative and systematic reviews, as well as the included articles. A research librarian at McMaster University was consulted for refining the search strategy. Two reviewers (T.I. and A.M.L.M.) independently screened titles and abstracts, reviewed full texts, extracted data and assessed the methodological quality of included studies. A piloted data extraction form was used to extract the data including the first author, publication years, journal name, study designs, settings (countries, regions, institutions, data sources, etc.), inclusion and exclusion criteria of study infants, definitions and numbers of late preterm infants and term infants, maternal and infant demographic characteristics, outcomes, time of assessment (e.g. < 28 days of age, < 1 year of age, etc.), statistical measures of association, and results including raw outcome data, and both unadjusted and adjusted effect estimates including odds ratios (ORs), relative risks (RRs), incident rate ratios (IRRs), and hazard ratios (HRs). The

corresponding authors of included studies were approached by email when their study data required clarification.

Criteria for Eligible Studies

This systematic review included cohort studies and case-control studies published as full-text articles that compared health service utilization after discharge home from the initial birth hospitalization between late preterm infants (34-36 weeks gestational age) and term infants (37-41 weeks gestational age). Studies using slight variations in the definition of late preterm or term infants were also included as long as the gestational age ranges were between 33 and 37 weeks for late preterm infants (e.g. 33-35 weeks, 35-37 weeks) and ≥ 36 weeks for term infants (e.g. 36-40 weeks, 39-41 weeks, ≥36 weeks). No restrictions on socioeconomic, geographic, or racial/ethnic characteristics of the study population were applied, but the studies were restricted to English-language articles to ensure adequate assessment of bias and quality.

Health Service Utilizations

The primary outcome was all-cause admissions after initial discharge home during the neonatal period (up to 30 days of age), infancy (up to 1 year), early childhood (from 1 up to 6 years), school age (from 6 up to 12 years) and adolescence (from 12 up to 18 years), and adulthood (above 18 years old). The secondary outcomes included cause-specific admissions, emergency department or outpatient visits, cause-specific emergency department or outpatient visits, use of special health care services including physical therapy, occupational therapy,

speech and language therapy, consultation with dieticians, etc., and use of home care visits (nurses, physicians, etc.).

Assessment of Methodological Quality Using Newcastle-Ottawa Scale (NOS)

A modified version of the Newcastle-Ottawa Scale (NOS)[9] was used to assess the methodological quality of the included studies. The NOS uses a '*star system'* in which a study is awarded one or two stars for each item and a score is given that ranges from zero up to nine stars.[9] These items encompass three quality dimensions including the selection of study groups, comparability of groups, and the ascertainment of outcome (for cohort studies) or exposure (for case-control studies).[9] Because the eligible infants cannot have the outcomes (post-discharge health service utilizations) at discharge, one of the items of the NOS, whether the infants have a history of outcomes at the start of the study, was deleted for both case-control and cohort studies. This was replaced by another item to evaluate whether the study included only infants who survived at discharge from birth hospitalizations rather than all late preterm births because those died before the discharge were not able to have the study outcomes (i.e. health service utilizations after initial discharge from birth hospitalizations). Multiple births (e.g. twins) was considered the most important confounder for the assessment of the comparability of groups. Delivery modes, race/ ethnicity, and socioeconomic status were considered other important confounders. Given that there are is no recommendations for specific cut-offs, studies with NOS $\geq$ 7 scores were considered of high quality as used in a previous report from the Agency for

Healthcare Research and Quality, USA.[10] Disagreements regarding the study selections and NOS assessments between the two reviewers (T.I. and A.S.) were resolved by discussion or consultation with an adjudicator (S.M.). The protocol for this systematic review was registered with PROSPERO (the registration number of CRD42016042401).[11]

Summary and Synthesis of Data and Statistical Analysis

The key characteristics of included studies were summarized in tables. The effect estimates in the included studies (e.g. OR and RR for binary outcomes, IRR for count outcomes, HR for time-to-event outcomes) were summarized and presented as forest plots for each outcome and, data permitting, meta-analyses were conducted by pooling adjusted effect estimates using generic inverse-variance methods with Review Manager software.[12] Because more studies reported the effect estimates as ORs rather than RRs, the RRs were converted to ORs based on the prevalence of the outcomes in the control groups (term infants) for meta-analyses.[13] When effect estimates were provided for subgroups of late preterm infants with the same reference term infants (e.g. 34 vs 38-41 weeks and 35-36 vs. 38-41 weeks), the summary effect estimates (e.g. 34-36 weeks vs. 38-41 weeks) were calculated assuming a moderate correlation of the effects between the subgroups of 0.5.[14] Heterogeneity among studies was assessed by a chi-square test of heterogeneity and I^2 statistics.[15] Publication bias was visually assessed using funnel plots.

Subgroup Analysis and Sensitivity Analysis

Subgroup analyses planned a priori were conducted for the primary outcome stratifying studies by an inclusion of only singletons, inclusion of multiple births with adjustment for multiple births, and inclusion of multiple births without the adjustment. Another pre-planned subgroup analysis assessed the effect of the slightly different definitions of gestational age for late preterm infants (lower gestational age limits of 33, 34, or 35-36 weeks) or term infants (lower gestational age limits of 37-38 or ≥ 39 weeks). The differences between subgroups were assessed by the Cochran's Q test and I^2 statistic using the Review Manager software.[15, 16] A priori planned sensitivity analysis was conducted to exclude low-quality studies to evaluate the robustness of the study results.

RESULTS

Among 3656 records after excluding duplicates in the literature search, the full texts of 228 articles were reviewed, and 52 studies were included in this systematic review (Figure 1). Two studies (Paul 2006, Maisels 1998)[17, 18] were case-control studies, and the others were cohort studies. Several articles were excluded because they used cohorts overlapping with those of other included articles that were more recent, larger, or of high-quality and did not add any new information to this systematic review (eTable 2). In these cases, one article was included to avoid duplication of results. The reasons for exclusion of some studies were described in eTable 3 when these reasons were not simple and required elaboration.

All-Cause Health Service Utilization

A total of 27 studies reported all-cause hospital admissions or emergency department visits (Table 1A). Two studies (Slimings 2014 and Srinivasjois 2015)[19, 20] used overlapping cohorts, but both were included in this systematic review because the former assessed the count of all-cause admissions providing IRR and the latter assessed any all-cause admissions providing RR. The follow-up lengths ranged from 7 days to 18 years of age. There were various types of cohorts (2 national and 10 regional population-based cohorts, 8 multicenter or database cohorts [e.g. Medicaid], 7 single-center cohorts) from various countries (12 studies from the United States of America, 3 from Australia, 3 from the United Kingdom, 2 from Turkey, and 2 from Canada and 1 study from: Taiwan, Japan, Brazil, India, and Spain). Among 18 studies conducting adjusted analyses, most studies (12 studies) used ORs as effect estimates. Relative risks and IRRs were reported in 3 studies.

Late preterm infants had higher chances of admission than term infants in all the time periods, from the neonatal period through adolescence (Figure 2A and 2B). The difference between late preterm and term infants decreased as the children grew from the neonatal period (adjusted OR 2.34 [95% confidence intervals 1.19, 4.61] and adjusted IRR 2.62 [2.52, 2.72]) to adolescence (adjusted OR 1.09 [1.04, 1.12], adjusted IRR 1.14 [1.11, 1.18]). Of note, the study population of Slimings 2014[20] in Figure 2B overlapped with that of Srinivasjois

2015[19] in Figure 2A. The sensitivity analysis including only high-quality evidence from studies with NOS ≥ 7 showed similar results (eFigure 1). A meta-analysis of unadjusted OR (eFigure 2) found similar results to the adjusted analyses. Funnel plots did not find serious publication biases.

Considerable heterogeneity existed in the meta-analyses for the neonatal period, infancy, and early childhood (I^2 = 78-100%, P values for chi-squared tests < 0.05; Figure 2A). The subgroup analysis stratifying by adjustment for multiple births (or excluding multiple births) found a significant subgroup difference when assessing outcomes during the neonatal period (P < 0.001; eFigure 3). The subgroup analysis stratifying studies based on whether early term infants (37-38 weeks gestational age) were included in the reference group found significant subgroup differences when assessing outcomes during infancy (P = 0.02; eFigure 4). Therefore, these factors may be the reasons for the heterogeneity, although the I^2 was still considerable in one of the subgroups (98-100%; eFigure 3 and 4). The subgroup analyses stratifying studies by the lower limit of gestational age for late preterm infants (33, 34, or 35-36 weeks) found significant subgroup differences in early childhood (P = 0.03; eFigure 5). Although the inclusion of younger, therefore likely at higher risk, preterm infants in the late preterm infant group was expected to increase the OR, the study including younger preterm infants (33 weeks gestational age) had smaller OR (1.35 [1.29-1.41]) than the other study including preterm infants at ≥34 weeks gestational age (OR 1.41 [1.39-1.47]).

There were additional studies evaluating all-cause admissions that were not included in the primary meta-analyses. Two studies reported higher odds of ≥ 2 or ≥ 3 admissions of late preterm than term infants (eTable 4).[21, 22] Three studies included only infants admitted to neonatal intensive care units during their initial birth hospitalizations and found increased admissions after discharge in late preterm infants compared with term infants (eTable 5).[23-25] One study assessed only infants who had critical congenital heart diseases and did not find significant difference in post-discharge admission rates between late preterm and term infants.[26]

There were fewer studies comparing emergency department visits of late preterm and term infants than those comparing admissions. Although the meta-analyses of unadjusted effect estimates showed a significant higher risk of emergency department visits in late preterm infants than term infants from the neonatal period to early childhood (eFigure 6), they were not significant in studies using adjusted analyses except for a borderline significance for the neonatal period (Figure 2C).

Cause-Specific Health Service Utilization

Twenty-six studies compared the cause-specific hospital utilizations among late preterm versus term infants (Table 1B). The causes of hospital utilizations included jaundice or hyperbilirubinemia (4 studies),[17, 18, 27, 28] non-jaundice causes (2 studies),[8, 29] respiratory problems (16 studies including 7

studies of respiratory syncytial virus [RSV] or bronchiolitis,[30-36] 1 study of respiratory viral infection,[37] 5 studies of asthma/wheezing,[38-42] and 3 studies of non-infectious respiratory problems[19, 28, 43]), infection (2 studies),[19, 28] neurological or psychological problems (3 studies),[19, 44, 45] and others.[46-48]

Due to high heterogeneity in the type of effect estimates, meta-analyses were not conducted for most of the causes except for jaundice, non-jaundice causes, and asthma in certain study periods (Figure 3A-3G).

Health service utilization for jaundice: Late preterm infants had higher odds of admission than term infants for jaundice in the neonatal period and infancy (Figure 3A). On the other hand, the admissions for non-jaundice causes were not significantly different between late preterm and term infants in the neonatal period (Figure 3B).

Health service utilization for respiratory or infectious problems: Most studies reported a significant increase in admissions for RSV or bronchiolitis of late preterm infants compared with term infants during infancy and early childhood (Figure 3C). Health service utilization for asthma was significantly increased in late preterm infants than term infants in the age group within 6 years of age (Figure 3D). The increase was not significant after 6 years in the single study assessing it. Admissions for non-infectious respiratory disease and those for infection were significantly increased in late preterm infants than term infants from the neonatal period through adolescence (Figure 3E and 3F).

Health service utilization for neurological or mental problems: Admissions for central nervous system diseases and those for mental or psychiatric disorders were significantly increased in late preterm infants than term infants from infancy through adolescence or adulthood (Figure 3G). One study reported increased admissions due to epilepsy in adulthood (25-37 years of age) in late preterm infants.

Health service utilizations for other problems: Srinivasjois 2015 reported increases in admissions for other causes including perinatal, oral, congenital, social, and renal problems for late preterm infants compared with term infants in certain time periods from the neonatal period through adolescence.[19] Other studies reported increased admissions for surgeries (up to 1 year of age),[28] acute gastroenteritis (up to 6 years of age),[47] and type 1 diabetes (up to 6 years of age)[46] as well as increased admissions or ED/outpatient visits for injuries (up to 12 years of age)[48] (Table 1B).

Other health service utilizations: Wilson 2012 found no significant difference when comparing the emergency department visits within 3 days of vaccination at 2 months of age between late preterm and term infants (crude IRR 1.09 [0.95, 1.25])[49] (Table 1C). Hwang 2013 reported that late preterm infants had more timely home or office follow-up visits within 1 week after initial discharge home than full-term infants (adjusted RR 1.07 [1.06, 1.08]).[50] Shapiro-Mendoza 2013 reported that late preterm infants had higher enrollment rates in early intervention services provided by developmental specialists, occupational

therapists, and speech-language pathologists and used more nursing services and physical therapy than term infants.[51]

DISCUSSION

To our knowledge, this systematic review is the first to summarize health service utilization after the initial birth hospitalizations of late preterm infants compared with term infants. After initial discharge, late preterm infants had higher rates than term infants of all-cause admissions that persisted from the neonatal period through adolescence, although the magnitude of the differences decreased as the infants grew up. In addition, late preterm infants had higher rates of cause-specific hospital service use than term infants, for jaundice, infections including specifically RSV or bronchiolitis, non-infectious respiratory problems, asthma, neurological problems, and mental health problems.

Previous systematic reviews of late preterm infants have focused mainly on short-term mortality and morbidities during the initial birth hospitalizations or the neonatal period and long-term neurodevelopmental, behavioral, or educational problems and growth. Teune et al (2011) [52] reported that compared to term infants, late preterm infants had increased mortality and morbidity during the initial birth-hospitalization including hypothermia, hypoglycemia, hyperbilirubinemia, infections, respiratory and neurological problems (e.g. seizures, intraventricular hemorrhage). In addition, the same systematic review found higher risks of cognitive deficit, cerebral palsy, and poor school

performance (e.g. not ready to start school, learning difficulty, and special education requirement) in late preterm infants than term infants, but an inconsistent risk for behavioral or psychological problems.[52] Other systematic reviews reported the similar findings on neurodevelopmental, behavioral, psychological, and educational problems of late preterm infants.[53, 54] Another systematic review by Colin et al (2010) found that the infants at 32 to 36 weeks gestational age had higher respiratory morbidity compared with term infants.[55] Unlike our systematic review, Colin et al (2010) included many studies assessing neonatal respiratory morbidity during the initial birth hospitalizations (e.g. respiratory distress syndrome), did not specifically assess health service utilization, and did not summarize the results by age (e.g. neonatal periods, infancy).[55]

This study had several strengths. First, a wide range of health service utilization was assessed including all-cause and specific-cause admissions, emergency department visits, and outpatient visits in various developmental stages from the neonatal period to adulthood. Second, where possible, meta-analyses were conducted to provide summary effect estimates to better quantify risk, and forest plots were created to facilitate the overview of the results across developmental stages. Third, sensitivity analyses showed the robustness of the findings, and the subgroup analyses assessed potential effect modifiers or factors causing heterogeneity. The OR for all-cause admissions in the neonatal period was significantly higher in the subgroup not adjusted for multiple births than that

adjusted for them indicating that multiple births were effect modifiers. It may be because multiple births had a higher risk of admissions[56] and late preterm infants had a higher proportion of multiple births than term infants.[57] In addition, the OR for all-cause admissions in the infancy was significantly higher in the subgroup including only full term infants in the control group than that including both early term and full term infants. This indicated that the inclusion of early term infants in the control group was one of the factors causing heterogeneity, and it may be because early term infants had a higher risk of admissions than full-term infants.[21] Although these factors might partially explain the observed heterogeneity, the considerable heterogeneity remained in all the subgroup analyses as well as in the sensitivity analysis and could not be resolved by inclusion of multiple births, differences in the gestational-age ranges of late preterm or term infants groups, and quality of evidence. Regional differences in health care provisions (e.g. discharge policies, insurance systems, accesses to health services) might partly play a role for the heterogeneity; however, the lack of detailed information in many studies prevented further exploration. Hence heterogeneity is also a limitation of our study. Other limitations include the fact that the nature of the exposure, late preterm birth, can be studied only through observational studies, which are susceptible to selection bias. Observation studies are also susceptible to confounding; hence, we focused on adjusted effect estimates for meta-analyses where possible. Second, variation in the types of effect estimates (e.g. OR, RR, HR, and IRR) and children's ages prevented us from conducting some meta-

analyses, particularly for cause-specific health service utilization. Third, data were limited regarding emergency department or outpatient visits of late preterm infants. Hence the increased utilization that was found is only the 'tip of the iceberg', with late preterm births having much larger system implications. Lastly, we restricted the inclusion of studies to the English language to ensure adequate assessment of bias and quality; however, the restriction itself may introduce bias.

The results of our systematic review will inform discussions between families of late preterm infants and health care providers. As recommended,[58] these risks of late preterm infants should be considered for deciding the timing of deliveries. Late preterm infants should be considered a vulnerable group who may need enhanced support throughout adolescence. Regional differences in health service provisions would be an important topic of future investigation, as should the prevention of late preterm birth.

CONCLUSION

This systematic review found that late preterm infants had a higher risk of all-cause hospital admissions after initial discharge home from the neonatal period through adolescence as well as higher use of various cause-specific health services in certain developmental stages. The differences in both the short- and long-term were quantified to inform discussions between care providers and families.

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Figures and Legends:

Figure 1: Flow diagram of literature search and study selection of systematic review of late preterm infant health service utilization
Figure 1 Legend: None.

Figure 2: Forest plots for all-cause hospital service utilizations of late preterm versus term infants of systematic review of late preterm infant health service utilization
Figure 2A: Adjusted odds ratios of all-cause admissions from the neonatal period through adolescence
Figure 2B: Adjusted incidence rate ratios of all-cause admissions from the neonatal period through adolescence
Figure 2C: Adjusted effect estimates of all-cause emergency department visits from the neonatal period to early childhood (without meta-analyses)
Legend for Figure 2A-2C:
The cohort of Slimings 2014 in Figure 2B overlapped with that of Srinivasjois 2016 in Figure 2A (See the result section for the reasons for inclusion of both the studies).
*: When the effect estimates were provided for subgroups of late preterm infants with the same reference term infants (e.g. 34 vs. 38-41 weeks and 35-36 vs. 38-41 weeks), the summary effect estimates (e.g. 34-36 weeks vs. 38-41 weeks) were calculated assuming a moderate correlation of the effects between the subgroups of 0.5.
**: The RRs were converted to ORs based on the prevalence of the outcomes in the control groups (term infants) for meta-analyses.
Abbreviations: 95%CI = 95% confidence intervals ; d = days; DCH = discharge home form the initial birth hospitalizations; EE = effect estimates; LPI = late preterm infants; TI = term infants; yr = year(s);

Figure 3: Forest plots for cause-specific hospital service utilizations of late preterm versus term infants of systematic review of late preterm infant health service utilization
Figure 3A: Jaundice in the neonatal period and infancy
Figure 3B: Non-jaundice causes in the neonatal period
Figure 3C: Respiratory syncytial virus or bronchiolitis from infancy to early childhood (without meta-analyses)
Figure 3D: Asthma or wheezing from early childhood to school age
Figure 3E: Non-infectious respiratory problems from the neonatal period to school age (without meta-analyses)
Figure 3F: Infection from the neonatal period through adolescence (without meta-analyses)
Figure 3G: Neurological or mental health problems from infancy to adulthood (without meta-analyses)

Legend for Figure 3A-3G:

Infection in the Figure 3f included both respiratory and non-respiratory infection.

*: When the effect estimates were provided for subgroups of late preterm infants with the same reference term infants (e.g. 34 vs. 38-41 weeks and 35-36 vs. 38-41 weeks), the summary effect estimates (e.g. 34-36 weeks vs. 38-41 weeks) were calculated assuming a moderate correlation of the effects between the subgroups of 0.5.

**: The RRs were converted to ORs based on the prevalence of the outcomes in the control groups (term infants) for meta-analyses.

Abbreviations: Adm = admission(s); CNS = central nervous system; d = day(s); DCH = discharge home; ED = emergency department visits; EE = effect estimates; HSU = health service utilization(s); Op = outpatient visit(s); yr = year(s); 95%CI = 95% confidence intervals.

Table 1A: Characteristics of studies reporting all-cause health service utilizations

	Study	Follow up	Time of HSU	Birth year	Countries (Regions/City)	Cohort	Inclusion	GA of Late preterm infants (weeks)	GA of Term infants (weeks)	N of late preterm infants	N of term infants	HSU	aEE	Variables adjusted for	NOS
Neonatal period	**Jaiswal 2011**[60]	7d	DCH - 7d	2009-2009	India (Hyderabad)	Single-center	Live births	34-36	37-41	363	2707	Adm	OR	Multiple births, delivery modes, SGA	**6**
	Maisels 1998[18]*	14d after DCH	14d after DCH	1988-1994	USA (Michigan)	Single-center	Live births	36	≥ 40	36	163	Adm	OR	Sex, DM, maternal smoking, prolonged ROM, fetal meconium, jaundice, breastfeeding, LOS, many others	**6**
	Oddie 2005[61]	28d	DCH - 28d	1998	UK (the former Northern Region)	Multi-center	Live births	35-37	38-40	653	6126	Adm	OR	Delivery modes, SES, maternal age, parity, birth weight, LOS, birth hospitals	**7**
	Tomashek 2006[62]	28d	DCH-28d	1998-2002	USA (Massachusetts)	Database (PELL)	Singletons (VD, ED only)	34-36	37-41	1004	24320	Adm/Op	RR	Sex, Parity, prenatal care use	**9**
	Tsai 2012[63]	28d	DCH-28d	2008-2009	Taiwan (Northern part)	Single-center	Live births	34-36	37-40	914	6507	Adm	NA	NA	**5**
	Young 2013[7]	28d	DCH-28d	2000-2010	USA (Utah)	Regional PB	Live births	34-36	39-42	19081	180144	Adm	OR	Unclear	**6**
	Kuzniewicz 2013[8]	30d	30d after DCH	2003-2012	USA (California)	Database (KPNC)	Live births	34-36	≥ 39	19494	212523	Adm/ED	OR	Race, SGA, LGA, maternal age, LOS	**8**
Infancy	**Santos 2008**[64]	3mo	DCH-3mo	2004	Brazil (Southern part)	Regional PB	Singletons	34-36	37-41	447	NA	Adm	RR	Maternal education, income, skin color, maternal age	**7**
	McDonald 2013[65]	4mo	DCH-4mo	2008-unknown	Canada (Calgary)	Regional PB	Singletons	34-36	≥ 38	77	1150	Adm	NA	NA	**4**
	McLaurin 2009[66]	1yr	15d after DCH, 15d after DCH to 1yr	2004	USA	Database (MMCCE)	Live births	33-36	≥ 37	1683	33745	Adm/LOS	NA	NA	**5**
	Bird 2010[67]	1yr	DCH-1yr	2001-2005	USA (Arkansas)	Database (Medicaid)	Singletons	34-36	37-42	5188	15503	Adm	OR	Race, maternal education, marital status, delivery modes, sex, maternal smoking, many others.	**7**

	Ray 2013[28]*	1yr	DCH-14d, DCH-30d, DCH-90d, DCH-1yr	1993-2005	USA (California)	Regional PB	Live births	34-36	40 (≥ 37)	517879	5943809	Adm	OR	Multiple births, race, maternal education, income, SGA, parity, birth year	**9**
	Goyal 2015[68]	1yr	DCH-1yr	2007-2010	USA (Ohio)	Database (OHVP)	Live births	34-36	≥ 37	165	1638	ED	IRR	Race, ethnicity, insurance, sex, maternal age, smoking, mental health problems,	**7**
	Patrick 2015[69]	1yr	30d after DCH, 1yr after DCH	2006-2009	USA (New York)	Regional PB	Live births	33-36	≥ 37	51748	700613	Adm	OR	Insurance, sex, LOS, LBW, neonatal comorbidities	**8**
	Demestre 2016[70]	1yr	DCH-1yr	2009	Spain (Barcelona)	Single-center	Live births	34-36	38-41	90	89	Adm	NA	NA	**4**
Early childhood	**Khan 2015[71]***	2yr	DCH-6mo, 6-12mo, 12-24mo	2009-2010	UK (East Midlands)	Regional PB	Live births	34-36	≥ 37	984	1258	Adm/ED/ Op/ Many others	NA	NA	**5**
	Berard 2012[72]	3yr	DCH-2yr, 2-3yr, DCH-3yr	1997-2000	Canada (Quebec)	Regional PB	Live births	33-36	≥ 37	2176	33 879	Adm/ED/ Op/ prescription	NA	NA	**8**
	Boyle 2012[21]	5yr	DCH-9mo, 9mo-5yr	2000-2002	UK	National PB (Random sample)	Live births	34-36	39-41	1107	12540	Adm	OR	Multiple births, maternal education, ethnicity, occupation, sex, marital status, maternal age, smoking, alcoholic, many others.	**7**
	Kato 2013[22]	5.5yr	0.5-2.5yr, 2.5-5yr	2001	Japan	National PB	Live births	34, 35, 36	39	1549	11692	Adm	OR	Multiple birth, parents' education, sex, maternal age, smoking	**7**
	Pittard 2013[73]	6yr	Birth-6yr	1996-2001	USA (South Carolina)	Database (Medicaid)	Live births	34-36	37-42	1956	23984	Adm/ED	IRR	Delivery modes, race/ethnicity, education, income, maternal age, rural residence	**7**
	Stephens 2015[74]	1-6yr	1-6yr	2001-2005	Australia (NSW)	Regional PB	Singletons	33-34, 35-36	39-40	3878, 12,665	218254	Adm	OR	Marital status, rural residence, maternal age, smoking, parity, onset of	**9**

														labor, public hospital	
	Slimings 2014[20]	18yr	DCH-28d, 29d-1yr, 1-5yr, 5-12yr, 12-18yr	1980-2010	Australia (Western Australia)	Regional PB	Singletons	34-36	39-41	34841	467795	Adm	IRR	Sex, birth year	**8**
	Srinivasjois 2015[19]*	18yr	DCH-28d, 29d-1yr, 1-5yr, 5-12yr, 12-18yr	1980-2010	Australia (Western Australia)	Regional PB	Singletons	34-36	≥ 39	37977	507677	Adm	RR	Sex, birth year	**8**
Special population	**Celik 2013[23]**	early after DCH	Early after DCH	2010-2011	Turkey (Ankara)	Single-center	NICU admissions	34-36	37-41	605 (admitted)	1477 (admitted)	Adm	NA	NA	**3**
	Escobar 1999[24]	14d after DCH	14d after DCH	1992-1995	USA (California)	Database (KPNC)	NICU admission	33-36	≥ 37	1741	3726	Adm	OR	SGA, high SNAP score, birth hospitals	**5**
	Costello 2010[26]	30d after DCH	30d after DCH	2002-2008	USA (Boston)	Single-center	Critical CHD	34-36	39-40	140	378	Adm	NA	NA	**4**
	Kalyoncu 2010[25]	2mo	DCH-2mo	2005-2007	Turkey (Samsun)	Single-center	NICU admitted LPI	34-36	37-41	252	252	Adm	NA	NA	**4**

*: Four studies (Khan 2015, Maisels 1998, Ray 2013, Srinivasjois 2015) also reported cause-specific health service utilizations (Pleas see the foot notes in the Table 1b for detail).

Abbreviations: Adm = admissions; aEE = adjusted effect estimates; d = days; CHD = congenital heart disease; DCH = discharge home from the birth-hospitalization; DM = (maternal) diabetes mellitus; ED = emergency department visits; GA = gestational age; HSU = health service utilization(s); IRR = incidence rate ratios; KPNC = Kaiser Permanente Northern California; LGA = large for gestational age; LOS = length of stay of the birth-hospitalizations; MMCCE = MedStat MarketScan Commercial Claims and Encounters database; mo = months; N = numbers; NA = not available; NICU = neonatal intensive care unit(s); NOS = Newcastle Ottawa Scale; NSW = New South Wales, OHVP = Ohio home visiting program, Op = outpatient visits: OR = odds ratios; PB = population-based; ROM = rupture of membrane; RR = risk ratios; PELL = Massachusetts Pregnancy to Early Life Longitudinal Data Project; SES = socioeconomic status; SGA = small for gestational age; SNAP = The Score for Neonatal Acute Physiology; USA = United States of America; WA = Western Australia, yr = years

Table 1B: Characteristics of studies reporting cause-specific health service utilizations

Dx	Study	Diagnoses	Follow up	Time of HSU	Birth year	Countries (Regions/ City)	Cohort	Inclusion	GA of late preterm infants (weeks)	GA of term infants (weeks)	N of late preterm infants	N of term infants	HSU	aEE	Variables adjusted for	NOS
Jaundice/ non-jaundice causes	**Paul 2006**[17]	Jaundice/ dehydration/ feeding problems	10 d	DCH-10d	1998-2002	USA (Pennsylvania)	Regional PB	Healthy singletons	35-36	39-40	600	3963	Adm	OR	Delivery modes, race, maternal age, DM, PIH, smoking, sex, LOS	**7**
	Burgos 2008[27]	Jaundice	14d	DCH-14d	1991–2000	USA (California)	Regional PB	Healthy live births	34, 35, 36	40	44992, 89443, 167400	1951360	Adm	OR	Delivery modes, maternal education, insurance, race/ethnicity, prenatal care, birth weight, sex, LOS, birth year	**8**
	Maisels 1998[18]	In addition to all-cause admissions, this study assessed the cause-specific admissions for jaundice in 14 days after DCH. See Figure 1A for other information.														
	Escobar 2005[29]	Non-jaundice causes	14d	14d after DCH	1998-2000	USA (Northern California)	Database (KPNC)	Live births	34-36	≥ 37	2153	30261			Maternal age, sex, race, SGA, SNAP-II score, birth facility, follow-up status	**7**
	Kuzniewicz 2013[8]	In addition to all-cause admissions, this study assessed the cause specific admissions for non-jaundice causes in 30 days after DCH. See Figure 1A for other information.														
Respiratory problems	**Haerskjold 2016**[30]	RSV	2yr	DCH-2yr	1997-2003	Denmark	National PB	Live births	33-35, 36	37-41	11193, 9815	360484	Adm	NA	NA	**7**
	Boyce 2000[31]	RSV	1yr	DCH-6mo, 6-12mo, DCH-12mo	1989-1993	USA (Tennessee)	Database (Medicaid)	Live births (no CLD, CHD)	33-36	≥ 37	4598 child-years	582459 child-years	Adm	IRR	Race, maternal education, smoking, sibling, sex, rural residence	**7**
	Paramore 2010[32]	RSV	1yr	1st RSV season	2004-2006	USA	Database (MMCCE)	Live births	33-34, 35-36	≥ 37	1509, 2762	84290	Adm/ ED	NA	NA	**6**
	Lanari 2015[33]	Bronchiolitis	1yr	DCH-1yr	2009-2012	Italy	Multi-center	Live births	33-34, 35-37	≥ 38	737, 767	706	Adm	HR	Sex	**6**
	Olabarrieta 2015[37]	Respiratory viral infection	1yr	DCH-1yr	2011-2012	Spain (Madrid)	Single-center	Live births	34-36	Term	113	1858	Adm/ LOS/ PICU	NA	NA	**4**

	Flaherman 2012[34]	Bronchiolitis	2yr	DCH-2yr	1996-2004	USA (Northern California)	Database (KPNC)	Live births	34-36	38-40	7969	86708	Adm/ Op	OR	Race/ethnicity, maternal age, parental asthma, sex, birth weight, SGA, CLD, congenital anomaly, siblings	**7**
	Greenberg 2014[35]	CAAP RSV-CAAP	2yr	DCH-2yr	2004-2011	Israel (Southern region)	Regional PB	Live births	33-34, 35-36	≥ 37	Not clear	111799	Adm	RR	Ethnicity	**7**
	Helfrich 2015[36]	RSV	2yr	DCH-3mo, 3-6mo, 6mo-1yr, 1-2yr, DCH-2yr	2005-2011	USA	Database (MHS)	Live births	33-36	≥ 37	25890	573645	Adm	HR	Sex, birth year	**7**
	Paranjothy 2013[43]	Respiratory disease	5yr	DCH-1yr, 1-5yr	1998-2008	UK (Wales)	Regional PB	Live births	33-34, 35-36	40-42	5060, 12889	171861	Adm	HR	Multiple births, delivery modes, SES, maternal age, parity, smoking, sex, congenital anomaly, Apgar score, NICU admissions	**9**
Asthma/ wheezing	**Odibo 2016[38]**	Asthma/ Bronchiolitis	5yr	3-5yr	2000-2003	USA (South Carolina)	Database (Medicaid)	Singleton	34-36	39-41	3476	25975	Adm/ ED/ Op	HR	Delivery modes, race/ethnicity, maternal education, maternal age, parity, smoking, marital status, sex, birth weight, neonatal morbidities, many others	**8**
	Escobar 2013[39]	Asthma/ Wheezing	5yr	DCH-1yr, 1-5yr, 4-5yr	1996-2004	USA (Northern California)	Database (KPNC)	Live births	34-36	38-40	4665	51049	Adm/ Op/ Prescription	HR	Race, maternal age, history of asthma, siblings, congenital anomaly, SGA, CLD, RSV or admissions for respiratory diseases in 1st year	**7**
	Haataja 2016[40]	Asthma (medication reimbursement)	7yr	DCH-7yr	199-2008	Finland	National PB	Live births	34-36	≥ 37	39332	965224	Adm/ Op	NA	Multiple births, delivery modes, maternal age, gravida, smoking, ART, DM, PROM,	**9**

															sex, NICU admissions, ventilator use, antibiotics use	
	Leung 2016[41]	Asthma/ Bronchitis/ Bronchiolitis	12yr	9d-2yr, 2-6yr, 6-12yr, 9d-6yr, 9d-12yr, 3-12yr, 5-12yr	1997-1997	China (Hong Kong)	Regional PB	Live births	34-36	39-40	336	4321	Adm	HR	Delivery modes, SES, maternal age, parental history of allergy, maternal birth place, smoking, sex, birth hospitals	**6**
	Dombkowski 2008[42]	Asthma/Wheezing	18yr	5-18yr	2001-200	USA (Michigan)	Database (Medicaid)	Live births	33-36	37-41	18467	104751	Adm/ ED/ Op/ Prescription	OR	Race, urban residence, sex, birth weight, age	**8**
Neurological problems	**Lindstrom 2009[45]**	Psychiatric disorders	29yr	13-29yr	1973-1979	Sweden	National PB	Live births	33-36	39-41	2037	450165	Adm	HR	SES, SGA, Apgar score, parental psychiatric disorders, age	**8**
	Crump 2011[44]	Epilepsy	37yr	25-37yr	1973-1979	Sweden	National PB	Live births	35-36	37-42	19025	583571	Adm	OR	Multiple births, maternal education, income, marital status, maternal age, birth orders, SGA, sex, parental history of epilepsy	**9**
Other causes	**Algert 2009[46]**	Type 1 Diabetes Melitus	6yr	0-3yr, 3-6yr	2000-2005	Australia (NSW)	Regional PB	Singletons	34-36	37-39	19711	221151	Adm	NA	Unclear	**7**
	Bentley 2016[47]	Acute gastroenteritis	6yr	DCH-6yr	2001-2011	Australia (NSW)	Regional PB	Singletons	33-36	39-42	38685	656692	Adm	HR	SES, maternal country of birth, smoking, parity, DM, PIH, sex, birth weight, LOS, infections	**6**
	Sun 2010[48]	Injuries	12yr	DCH-12yr	1978-2004	Denmark	National PB	Singletons	33-36	39-41	55382	1105894	Adm/ ED/Op	IRR	Parental education, income, nationality, marital status, residential place, maternal age, parity, sex, birth year	**9**

Multiple causes	**Ray 2013[28]**	In addition to all-cause admissions, this study assessed the cause-specific admissions for non-infectious respiratory problems, respiratory infection, bacterial infection, non-specific infection, gastrointestinal or feeding problems, hyperbilirubinemia, surgical problems, and other problems in DCH-14d, DCH-30d, DCH-90d, and DCH-1yr. See Figure 1A for other information.
	Srinivasjois 2015[19]	In addition to all-cause admissions, this study assessed the cause-specific admissions for non-infectious respiratory problems, infection, CNS and mental disorders, social problems, perinalal and congenital disorders, oral, gastrointestinal, and renal problems, injuries, neoplasm, pregnancy problems, and other problems in DCH-28d, 29d-1yr, 1-5yr, 5-12yr, and 12-18yr. See Figure 1A for other information.

Abbreviations: Adm = admissions; ART = assisted reproduction technology, aEE = adjusted effect estimates; CLD = chronic lung disease; d = days; DCH = discharge home from the birth-hospitalization; DM = maternal diabetes mellitus; Dx = diagnosis categories; ED = emergency department visits; GA = gestational age; HR = hazard ratios; HSU = health service utilization(s); KPNC = Kaiser Permanente Northern California; LOS = length of stay of the birth-hospitalizations; MHS = Military Health System database; MMCCE = MedStat MarketScan Commercial Claims and Encounters database; mo = months; N = numbers; NA = not available; NICU = neonatal intensive care units; NOS = Newcastle Ottawa Scale; Op = outpatient visits: OR = odds ratios; PB = population-based; PIH = pregnancy-induced hypertension; PROM = premature rupture of membrane; RR = risk ratios; RSV = Respiratory Syncytial Virus; SES = socioeconomic status; SGA = small for gestational age; SNAP = Score for Neonatal Acute Physiology ; UK = United Kingdom; USA = United States of America; yr = years

Table 1C: Characteristics of studies reporting special health service utilizations

Studies	Special HSU	Follow up	Birth year	Countries (Regions/City)	Cohort	Inclusion	GA of late preterm infants (weeks)	GA| of term infants (weeks)	N of late preterm infants	N of term infants	NOS
Wilson 2012[49]	Post vaccination ED visits	3d post-vaccination	2002-2009	Ontario, Canada	Regional PB	Live births	33-36	≥ 37	49220	714841	**7**
Hwang 2013[50]	Timely post-discharge follow-up visits	7d of DCH	2000-2008.	USA	National PB (Random sample)	Singletons	34-36	39-41	31493	140964	**7**
Shapiro-Mendoza 2013[51]	Use of early intervention program services	0-3 yr	1998-2005	Massachusetts, USA	Regional PB	Singletons	34-36	39-41	27345	411567	**9**
Khan 2015[71]	In addition to all-cause health service utilization, this study assessed a routine 6 week check, health visitor visits, hearing or developmental checks, general physician visits, practice nurse visits, community pediatrician visits, physiotherapy visits, speech & language therapist visits, occupational therapist visits, community nurse visits, walk in centre contacts, telephone call to NHS Direct, other services in DCH-6 months, 6-12 months, or 12-24 months of age. See Figure 1A for other information.										

Abbreviations: Adm = admissions; d = days; DCH = discharge home from the birth-hospitalization; ED = emergency department visits; EI program = early intervention program; GA = gestational age; HSU = health service utilization(s); N = numbers; NHS = national health service; NOS = Newcastle Ottawa Scale; Op = outpatient visits: PB = population-based; USA = United States of America; yr = years

Figure 1: Flow diagram of literature search and study selection of systematic review of late preterm infant health service utilization

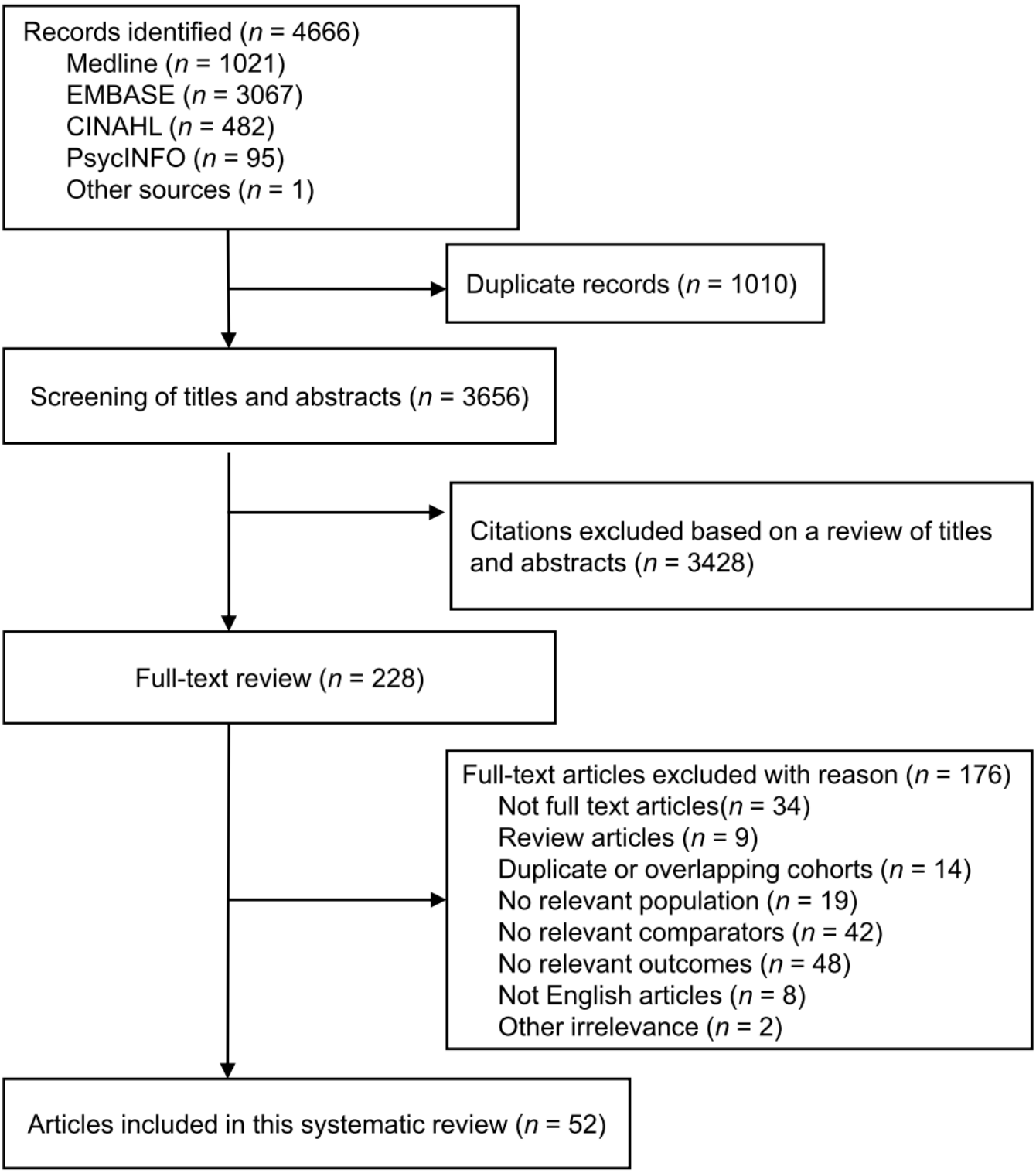
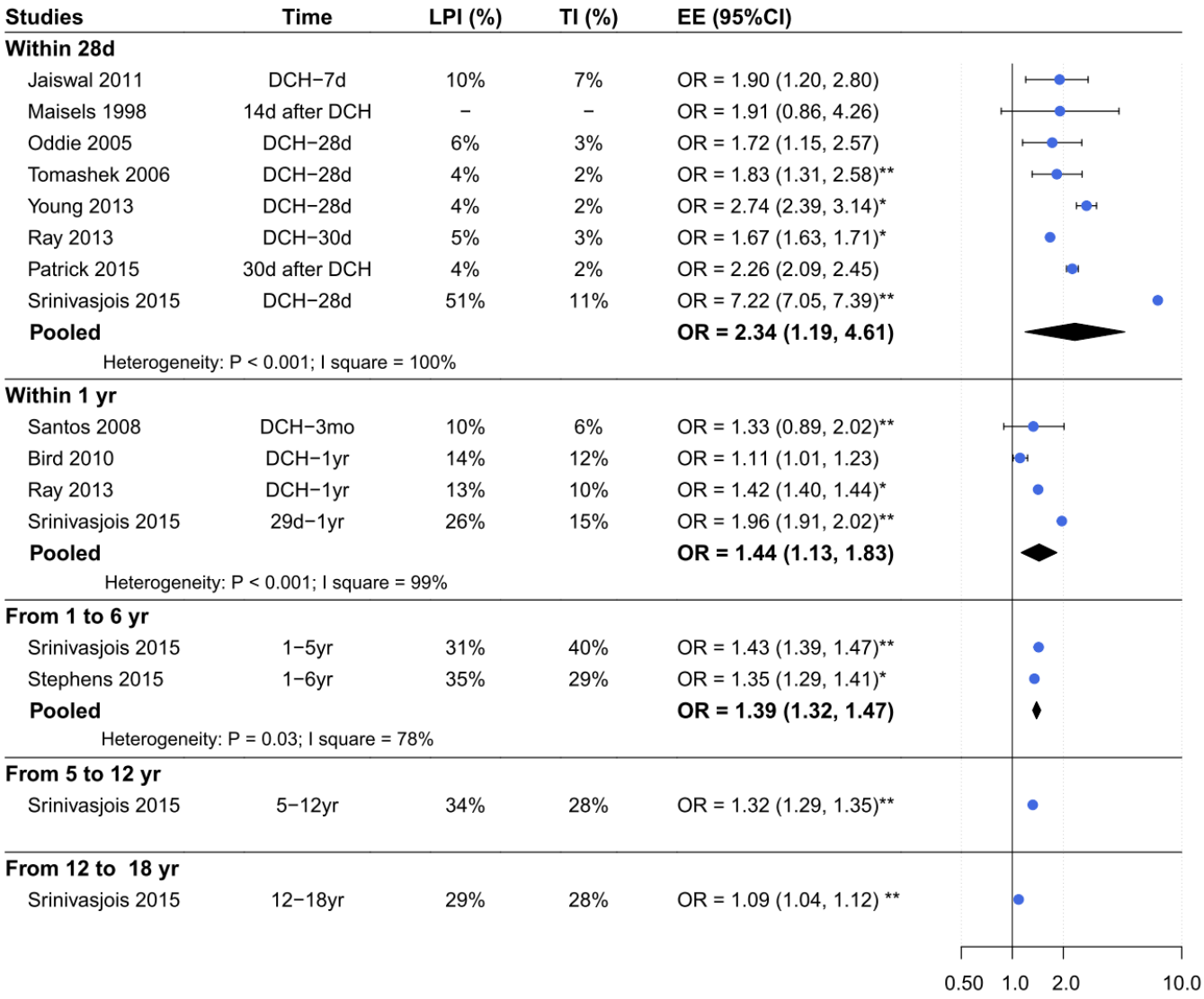
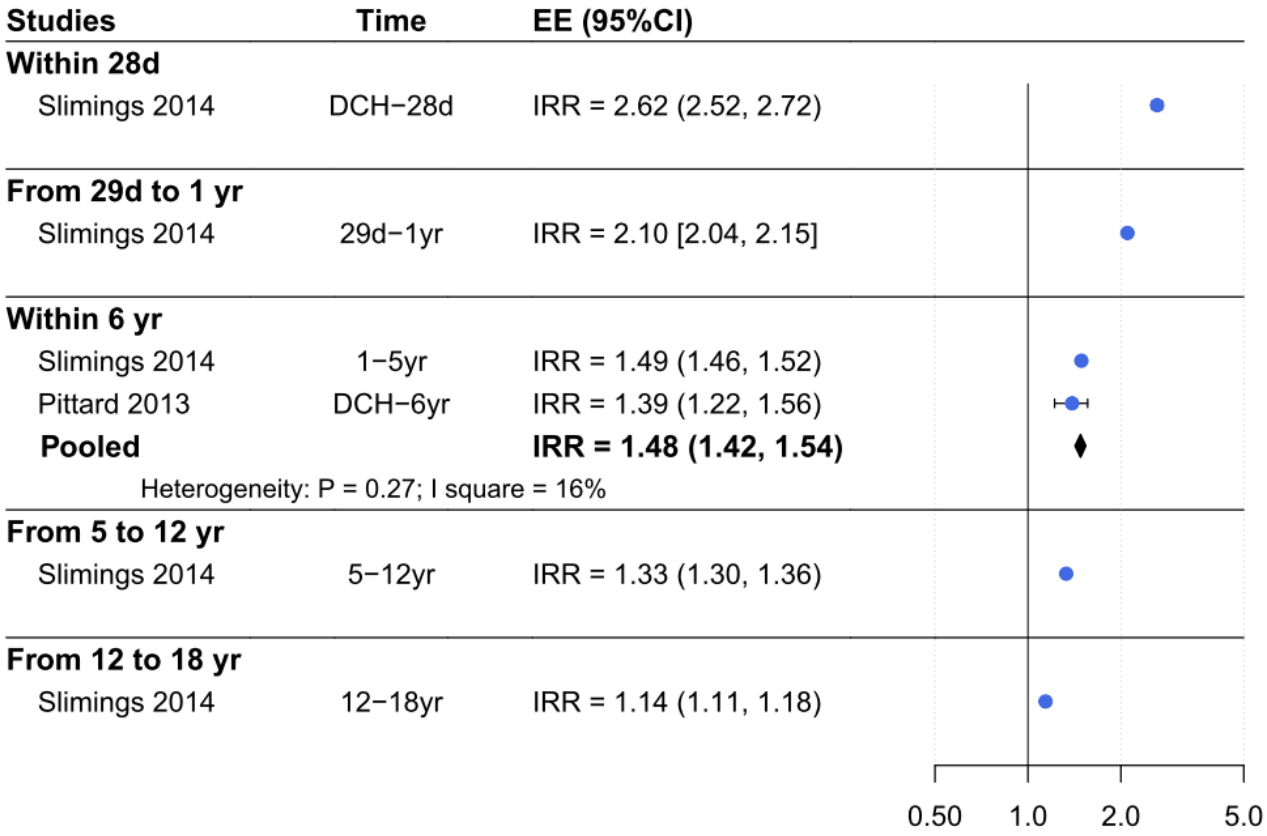


Figure 2: Forest plots for all-cause hospital service utilizations of late preterm versus term infants of systematic review of late preterm infant health service utilization

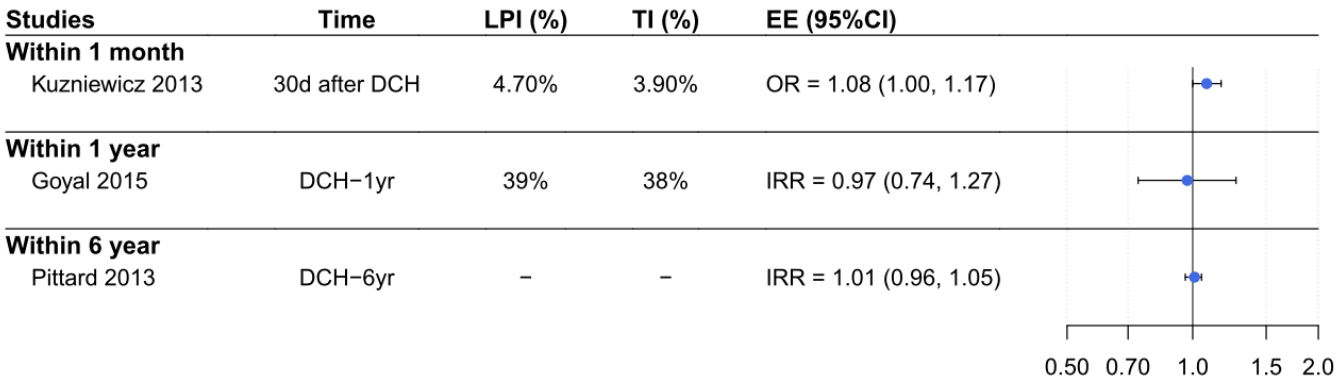
a) Adjusted odds ratios of all-cause admissions from the neonatal period through adolescence



b) Adjusted incidence rate ratios of all-cause admissions from the neonatal period through adolescence



c) Adjusted effect estimates of all-cause emergency department visits from the neonatal period to early childhood (without meta-analyses)



Legend for Figure 2A-2C

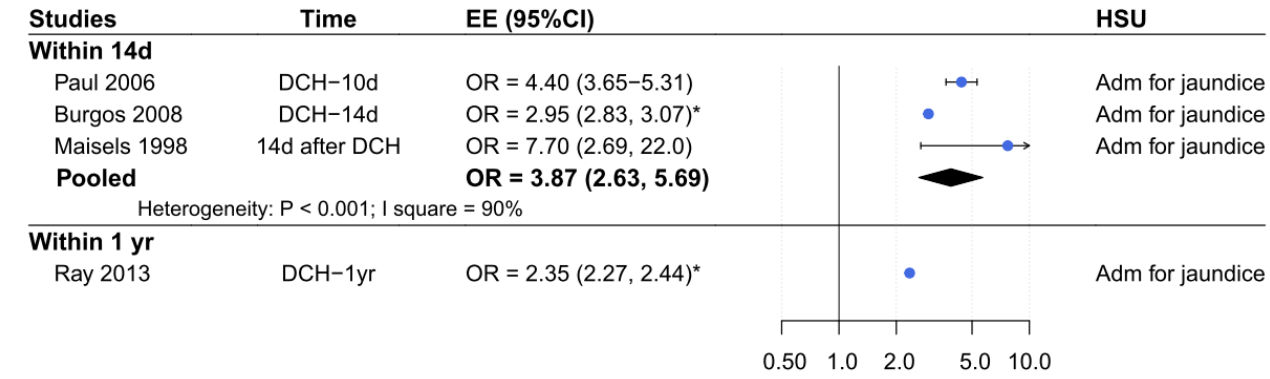
The cohort of Slimings 2014 in Figure 2B overlapped with that of Srinivasjois 2016 in Figure 2A (See the result section for the reasons for inclusion of both the studies).

*: When the effect estimates were provided for subgroups of late preterm infants with the same reference term infants (e.g. 34 vs. 38-41 weeks and 35-36 vs. 38-41 weeks), the summary effect

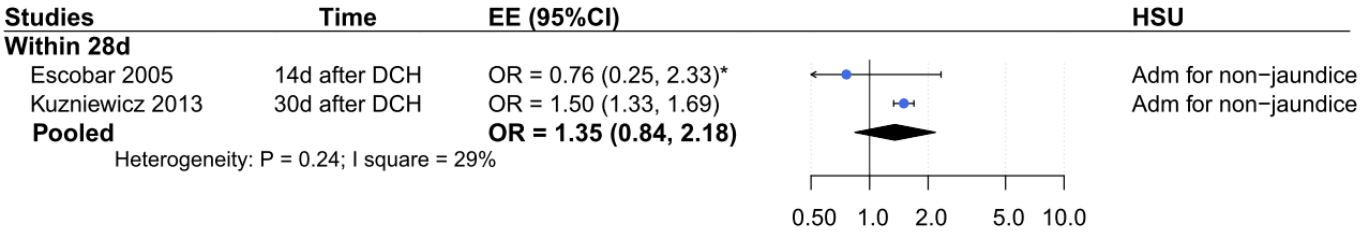
estimates (e.g. 34-36 weeks vs. 38-41 weeks) were calculated assuming a moderate correlation of the effects between the subgroups of 0.5.
**: The RRs were converted to ORs based on the prevalence of the outcomes in the control groups (term infants) for meta-analyses.
Abbreviations: 95%CI = 95% confidence intervals ; d = days; DCH = discharge home form the initial birth hospitalizations; EE = effect estimates; LPI = late preterm infants; TI = term infants; yr = year(s);

Figure 3: Forest plots for cause-specific hospital service utilizations of late preterm versus term infants of systematic review of late preterm infant health service utilization

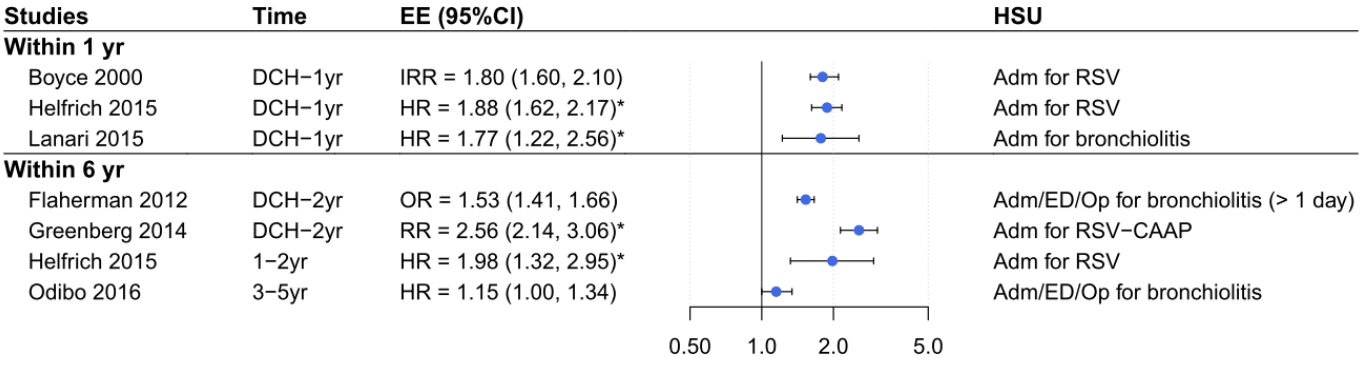
a) Jaundice in the neonatal period and infancy



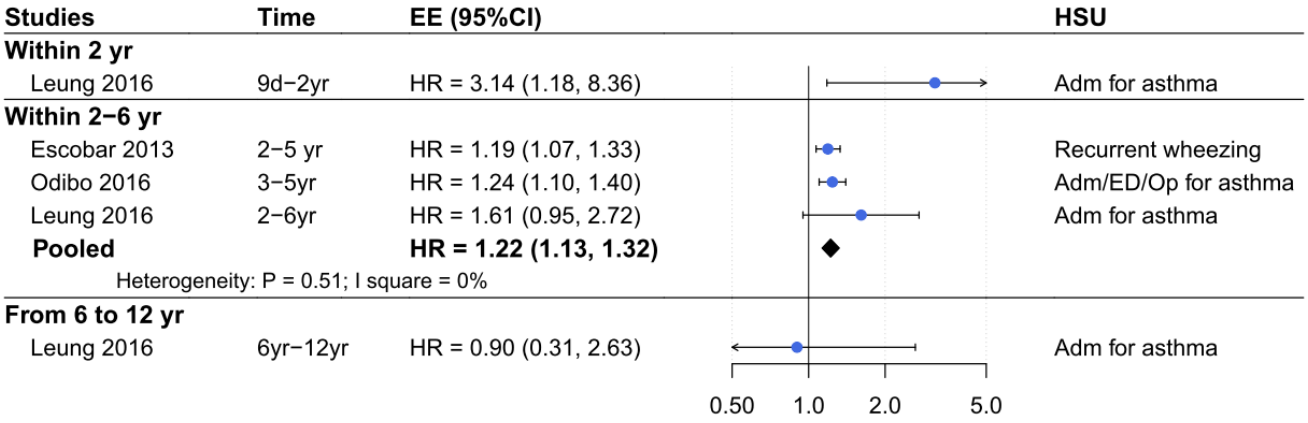
b) Non-jaundice causes in the neonatal period



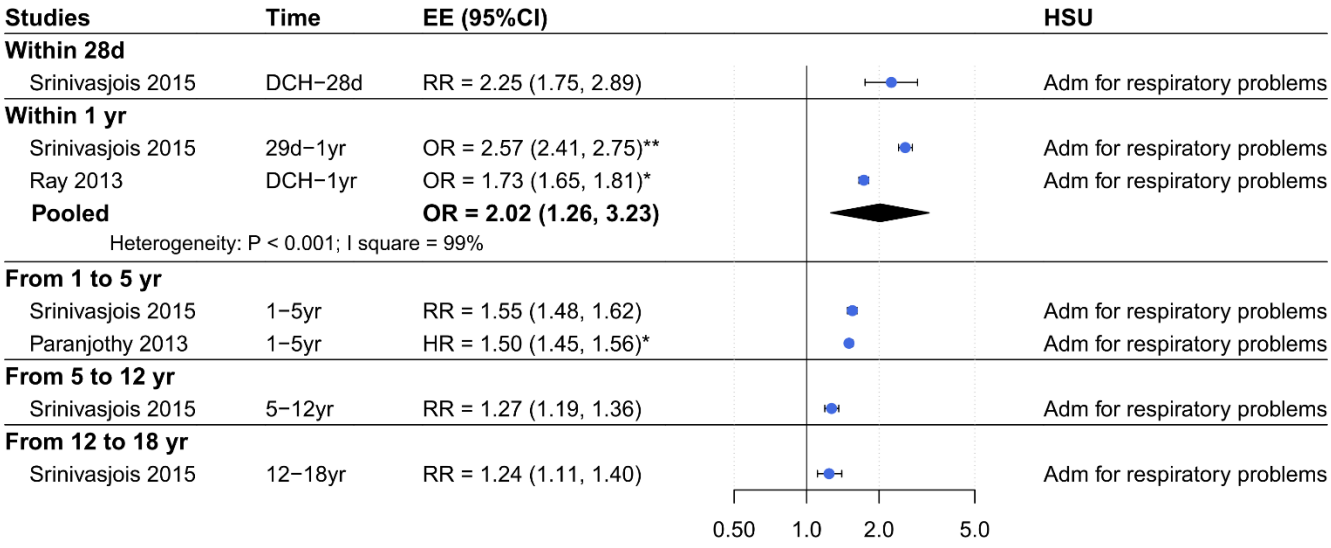
c) Respiratory syncytial virus or bronchiolitis from infancy to early childhood (without meta-analyses)



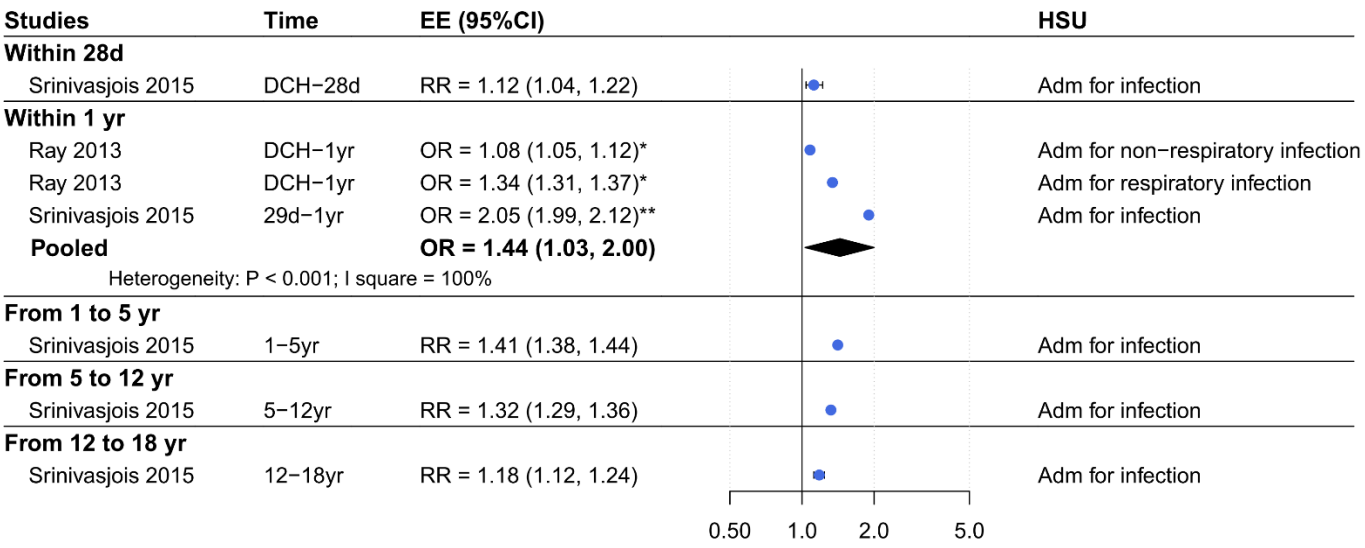
d) Asthma or wheezing from early childhood to school age



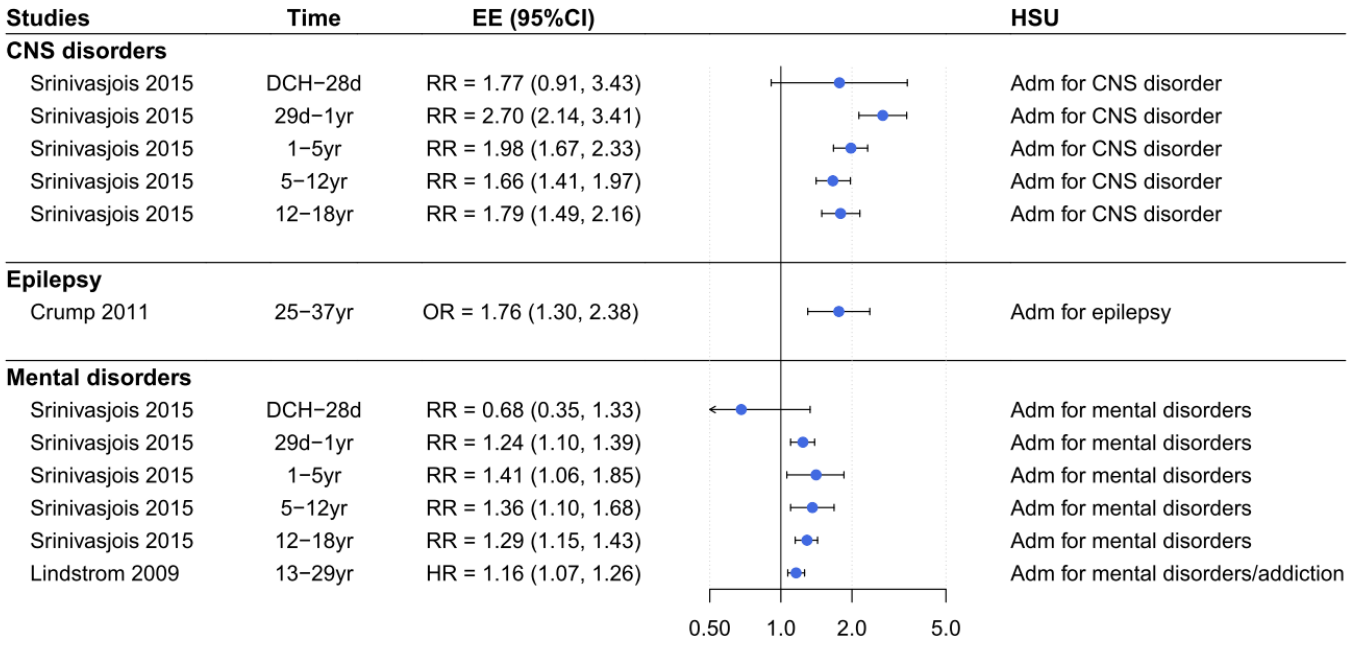
e) Non-infectious respiratory problems from the neonatal period to school age (without meta-analyses)



f) Infection from the neonatal period through adolescence (without meta-analyses)



g) Neurological or mental health problems from infancy to adulthood (without meta-analyses)



Legend for Figure 3A-3G.
Infection in the Figure 3f included both respiratory and non-respiratory infection.
*: When the effect estimates were provided for subgroups of late preterm infants with the same reference term infants (eg, 34 vs. 38-41 weeks and 35-36 vs. 38-41 weeks), the summary effect estimates (eg, 34-36 weeks vs. 38-41 weeks) were calculated assuming a moderate correlation of the effects between the subgroups of 0.5.
**: The RRs were converted to ORs based on the prevalence of the outcomes in the control groups (term infants) for meta-analyses.

Abbreviations: Adm = admission(s); CNS = central nervous system; d = day(s); DCH = discharge home; ED = emergency department visits; EE = effect estimates; HSU = health service utilization(s); Op = outpatient visit(s); yr = year(s); 95%CI = 95% confidence intervals.

Supplement

Contents

eTable 1: Search strategies for 4 databases (MEDLINE, EMBASE, CINAHL, and PsycINFO)

a) MEDLINE

#	Terms	Hit#
1	exp Hospitalization/	188181
2	exp Emergency Service, Hospital/	58850
3	exp Ambulatory Care/	48496
4	exp Outpatient Clinics, Hospital/	16288
5	exp Health Care Costs/	53751
6	exp Health Expenditures/	17711
7	exp Child Health Service/	21441
8	exp House calls/	2823
9	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8	371150
10	hospital admission*.mp.	28417
11	readmission*.mp.	20077
12	re admission*.mp.	1354
13	hospitalization*.mp.	163458
14	rehospitalization*.mp.	3712
15	re hospitalization*.mp.	679
16	((emergen* or er or ed or outpatient* or health service* or ambulatory* or hospital care* or health care* or health service* or hospital service*) adj3 (use* or visit* or utilization* or access* or cost*)).mp.	164871
17	10 or 11 or 12 or 13 or 14 or 15 or 16	344983
18	exp Rehabilitation/	170902
19	exp Physical Therapy Modalities/	126139
20	exp Occupational Therapy/	11476
21	exp Home Care Services/	42705
22	Rehabilitat*.mp.	146435
23	physiotherap*.mp.	19086
24	physical therap*.mp.	44497
25	occupational therap*.mp.	16068
26	speech therap*.mp.	7290
27	language therap*.mp.	2389
28	(home adj2 (visit* or care*)).mp.	54037
29	18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28	425783
30	9 or 17 or 29	942923
31	late preterm*.mp.	1192
32	late prematur*.mp.	67
33	near term.mp.	4522
34	moderate preterm*.mp.	84
35	moderate prematur*.mp.	21
36	((late or moderat*) adj3 (preterm* or prematur*)).mp.	2036

37	31 or 32 or 33 or 34 or 35 or 36	6502
38	exp Infant, Newborn/	547181
39	infant*.mp.	1128927
40	neonat*.mp.	245108
41	newborn*.mp.	684248
42	baby.mp.	31893
43	babies.mp.	31361
44	preemie*.mp.	108
45	38 or 39 or 40 or 41 or 42 or 43 or 44	1326144
46	37 and 45	3145
47	(("33" or "34" or "35" or "36") adj3 week*).mp.	31813
48	week* gestation*.mp.	26285
49	(week* adj3 (gestation* or GA)).mp.	57976
50	48 or 49	57976
51	45 and 47 and 50	9668
52	46 or 51	12132
53	30 and 52	1021

b) EMBASE

#	Terms	Hit#
1	exp hospitalization/	265791
2	exp child hospitalization/	9828
3	exp emergency health service/	80350
4	exp ambulatory care/	43210
5	exp "health care cost"/	239528
6	exp child health care/	74278
7	1 or 2 or 3 or 4 or 5 or 6	676005
8	hospital admission*.mp.	154931
9	readmission*.mp.	38809
10	re admission*.mp.	3143
11	hospitalization*.mp.	333704
12	rehospitalization*.mp.	5664
13	re hospitalization*.mp.	1982
14	((emergen* or er or ed or outpatient* or health service* or ambulatory* or hospital care* or health care* or health service* or hospital service*) adj3 (use* or visit* or utilization* or access* or cost*)).mp.	311545
15	8 or 9 or 10 or 11 or 12 or 13 or 14	753371
16	exp rehabilitation/	307468
17	exp physiotherapy/	72755
18	exp occupational therapy/	21024
19	Rehabilitat*.mp.	247437

20	physiotherap*.mp.	91787
21	physical therap*.mp.	27513
22	occupational therap*.mp.	28169
23	speech therap*.mp.	15159
24	language therap*.mp.	2204
25	(home adj2 (visit* or care*)).mp.	70833
26	16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25	572145
27	7 or 15 or 26	1497999
28	late preterm*.mp.	1745
29	late prematur*.mp.	118
30	near term.mp.	5959
31	moderate preterm*.mp.	123
32	moderate prematur*.mp.	31
33	((late or moderat*) adj3 (preterm* or prematur*)).mp.	2900
34	28 or 29 or 30 or 31 or 32 or 33	8769
35	newborn/	545608
36	infant/	613677
37	infant*.mp.	887166
38	neonat*.mp.	305912
39	newborn*.mp.	657007
40	baby.mp.	63445
41	babies.mp.	48355
42	preemie*.mp.	133
43	35 or 36 or 37 or 38 or 39 or 40 or 41 or 42	1371293
44	34 and 43	4171
45	(("33" or "34" or "35" or "36") adj3 week*).mp.	45790
46	week* gestation*.mp.	35035
47	(week* adj3 (gestation* or GA)).mp.	79073
48	46 or 47	79073
49	43 and 45 and 48	12799
50	44 or 49	16014
51	27 and 50	3067

c) CINAHL

#	Terms	Hit#
1	(MH "Hospitalization+")	
2	(MH "Emergency Service+")	37,894
3	(MH "Ambulatory Care")	8,974
4	(MH "Outpatient Service")	5,766
5	(MH "Health Care Costs+")	37,981

6	(MH "Child Health Services+")	15,272
7	(MH "Adolescent Health Services")	2,125
8	(MH "Home Visits")	4,600
9	(MH "Home Health Care+")	36,699
10	S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9	201,213
11	hospital admission*	11,035
12	readmission*	9,698
13	re admission*	420
14	hospitalization*	39,825
15	rehospitalization*	1,155
16	re hospitalization*	198
17	((emergen* or er or ed or outpatient* or health service* or ambulatory* or hospital care* or health care* or health service* or hospital service*) N3 (use* or visit* or utilization* or access* or cost*))	130,169
18	S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17	177,434
19	(MH "Rehabilitation+")	204,250
20	(MH "Physical Therapy+")	99,025
21	(MH "Pediatric Physical Therapy")	1,649
22	(MH "Occupational Therapy")	15,918
23	(MH "Pediatric Occupational Therapy")	2,126
24	(MH "Home Health Care+")	36,699
25	Rehabilitat*	131,377
26	physiotherap*	14,388
27	physical therap*	48,752
28	occupational therap*	32,945
29	speech therap*	5,002
30	language therap*	3,467
31	(home N2 (visit* or care*))	42,848
32	S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25 OR S26 OR S27 OR S28 OR S29 OR S30 OR S31	344,722
33	S10 OR S18 OR S32	596,591
34	late preterm*	822
35	late prematur*	85
36	near term	653
37	moderate preterm*	118
38	moderate prematur*	39
39	((late or moderat*) N3 (preterm* or prematur*))	989
40	S34 OR S35 OR S36 OR S37 OR S38 OR S39	1,695
41	(MH "Infant, Newborn+")	95,947
42	infant*	205,411
43	neonat*	46,494

44	newborn*	96,586
45	baby	21,314
46	babies	21,314
47	preemie*	187
48	S41 OR S42 OR S43 OR S44 OR S45 OR S46 OR S47	229,534
49	S40 AND S48	1,238
50	(("33" or "34" or "35" or "36") N3 week*)	5,822
51	week* gestation*	11,297
52	(week* N3 (gestation* or GA))	10,657
53	S51 OR S52	11,407
54	S48 AND S50 AND S53	2,415
55	S49 OR S54	3,332
56	S33 AND S55	482

d) PsycINFO

#	Terms	Hit#
1	exp HOSPITALIZATION/	19804
2	exp Hospital Admission/	4442
3	exp Emergency Services/	6543
4	outpatients/	6123
5	exp Outpatient Treatment/	5829
6	exp health care costs/	8279
7	exp Health Care Utilization/	13374
8	exp health care delivery/	32917
9	exp Home Visiting Programs/	1453
10	exp Home Care/	5415
11	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10	85524
12	hospital admission*.mp.	6748
13	readmission*.mp.	2657
14	re admission*.mp.	165
15	hospitalization*.mp.	29289
16	rehospitalization*.mp.	1282
17	re hospitalization*.mp.	154
18	((emergen* or er or ed or outpatient* or health service* or ambulatory* or hospital care* or health care* or health service* or hospital service*) adj3 (use* or visit* or utilization* or access* or cost*)).mp.	38151
19	12 or 13 or 14 or 15 or 16 or 17 or 18	70910
20	exp REHABILITATION/	65618
21	exp physical therapy/	2246
22	exp Occupational Therapy/	5195

23	exp Health Care Services/	94189
24	rehabilitat*.mp.	81222
25	physiotherap*.mp.	2475
26	physical therap*.mp.	4262
27	occupational therap*.mp.	9829
28	speech therap*.mp.	5774
29	language therap*.mp.	1689
30	(home adj2 (visit* or care*)).mp.	14019
31	20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30	201101
32	11 or 19 or 31	276464
33	late preterm*.mp.	167
34	late prematur*.mp.	8
35	near term.mp.	377
36	moderate preterm*.mp.	6
37	moderate prematur*.mp.	4
38	((late or moderat*) adj3 (preterm* or prematur*)).mp.	292
39	33 or 34 or 35 or 36 or 37 or 38	669
40	infant*.mp.	82310
41	neonat*.mp.	18379
42	newborn*.mp.	9815
43	baby.mp.	9961
44	babies.mp.	5488
45	preemie*.mp.	10
46	40 or 41 or 42 or 43 or 44 or 45	103804
47	(("33" or "34" or "35" or "36") adj3 week*).mp.	1934
48	week* gestation*.mp.	1450
49	(week* adj3 (gestation* or GA)).mp.	2857
50	48 or 49	2857
51	46 and 47 and 50	451
52	39 or 51	1050
53	32 and 52	95

eTable 2: Overlapping cohorts

Databases, regions, countries for the cohorts	Included studies (Health service use assessed)	Excluded studies** (Health service use assessed)
USA cohorts		
Kaiser Permanente Northern California (KPNC)*	Flaherman 2012 (Adm/Op for bronchiolitis),[1] Escobar 2005 (Adm for non-jaundice causes),[2] Escobar 2013 (Adm/Op/Prescription for asthma/wheezing),[3] Kuzniewicz 2013 (Adm/ED for any cause) [4]	Escobar 2006 (Adm for any causes),[5] Escobar 2010 (Adm for for asthma/wheezing),[6] Flaherman 2010 (Adm/Op for bronchiolitis)[7]
California (PB)*	Burgos 2008 (Adm for jaundice),[8] Ray 2013 (Adm for any cause)[9]	
Massachusetts, USA (PB)	Tomashek 2006 (Adm/Op for any cause),[10] Shapiro-Mendoza 2013 (Use of early intervention program services) [11]	Clements 2007 (Use of early intervention program services)[12]
MedStat MarketScan Commercial Claims and Encounters database	McLaurin 2009 (Adm/LOS for any causes),[13] Paramore 2010 (Adm/ED for RSV) [14]	
South Carolina, USA (PB)	Pittard 2013 (Adm/ED for any causes),[15] Odibo 2016 (Adm/ED/Op for asthma/bronchiolitis)[16]	
European cohorts		
Denmark (PB)	Sun 2010 (Adm/ED/Op for injuries),[17] Haerskjold 2016 (Adm for RSV)[18]	Yuan 2001 (Adm for infections in 2 regions in Denmark) [19]
Finland (PB)	Haataja 2016 (Adm/Op for asthma)[20]	Hirvonen 2014 (Adm due to cerebral palsy.) [21]
Italy (30 centre)	Lanari 2015 (Adm for bronchiolitis)[22]	Lanari 2011 (Adm for lower respiratory infection),[23] Lanari 2013[a] (Adm for bronchiolitis),[24] Lanari 2013b (Adm for bronchiolitis) [25]
Sweden (PB)	Lindstrom 2009 (Adm for psychiatric disorders),[26] Crump 2011(Adm for epilepsy)[27]	
Other cohorts		
Western Australia (PB)	Slimings 2014 (Adm for any causes [IRR]),[28] Srinivasjois 2016 (Adm for any cause [RR], Adm for various causes including respiratory problems, infection,	Moore 2010 (Adm for acute lower respiratory infection),[30] Miller 2016 (Adm for infection)[31]

	etc.)[29]	
New South Wale, Australia (PB)	Algert 2009 (Adm for type 1 diabetes mellitus),[32] Stephens 2015 (Adm for any causes),[33] Bentley 2016 (Adm for acute gastroenteritis)[34]	
Pelotas, Brazil (PB)	Santos 2008 (Adm for any causes)[35]	Barros 2012 (Adm for any causes)[36]

*: The KPNC cohorts were in California and therefore overlapped with two California population-based cohort studies (Burgos 2008, Ray 2013). Escobar 1999 included in this study was also the KPNC cohort but was not included in the table because the birth days of infants (1992-1995) did not overlap with other KPNC cohorts (1996-2004).

**: See the eTable 3 for the detailed reasons for the exclusion.

Abbreviations: Adm = admissions; ED = emergency department visits; Op = outpatient visits; IRR = incidence rate ratios; PB = population-based cohorts; RR = relative risks; USA = the United States of America.

eTable 3: Excluded studies with specific reasons

Studies	Reasons for exclusions
Barros 2012 [36]	This study was excluded due to overlap with another study included (Santos 2008).[35] Santos 2008 reported admissions in DCH-3mo but had higher quality (NOS =7) with good follow-up (97%). Barros 2012 reported admissions in DCH-1yr but very poor quality (NOS = 5) with poor follow up (38% for adjusted analysis).
Clements 2007 [12]	This study cohort overlapped with another larger more recent study included in our SR (Shapiro-Mendoza 2013). [11]
Escobar 2005 [2]	This study cohort overlapped with another larger more recent study included in our SR (Ray 2013).[9]
Escobar 2006 [5]	This study cohort overlapped with another larger study included in our SR (Ray 2013).[9]
Escobar 2010 [6]	This study cohort overlapped with another more recent study included in the SR (Escobar 2013).[3] Both studies assessed asthma/wheezing.
Flaherman 2010 [7]	This study cohort overlapped with another study included (Flaherman 2012)[1] and included no additional information.
Goyal 2011 [37]	This study reported asthma, persistent asthma, and acute outpatient visits with wheeze in late preterm infants compared with term infants. However, assessment was based on any diagnosis in electric health records (asthma was not necessarily a primary diagnosis).
Henckel 2004 [38]	This study assessed admissions due to respiratory syncytial virus infections but did not compare late preterm infants with term infants.
Hirvonen 2014 [21]	This study was excluded because it included only infants diagnosed as having cerebral palsy and assessed the admission due to cerebral palsy. The author was contacted and confirmed it.
Kuzniewicz 2013 [4] (A part of the study data)	This study cohort overlapped with another study (Ray 2013).[9] Therefore, the data on all-cause admissions were excluded from this systematic review. However, this study also reported admissions for non-jaundice causes and all-cause ED visits that Ray 2013 did not assess. Therefore, these data were included in this systematic review.
Lanari 2011 [23]	This study cohort overlapped with another more recent study that we included in our SR (Lanari 2015).[22]
Lanari 2013a [24]	This study cohort overlapped with another study included (Lanari 2015)[22] and did not add new information for this systematic review.
Lanari 2013b [25]	This study cohort overlapped with another study included in our SR (Lanari 2015)[22]. The study also did not contain any new information for this systematic review.
Miller 2016 [31]	This study cohort overlapped with another study included (Srinivasjois 2016)[29] and did not add new information for this systematic review.
Moore 2010 [30]	This study cohort overlapped with another study that we included (Srinivasjois 2016).[29] The outcomes assessed in this study (acute lower respiratory infections)

	also overlapped with those in Srinivasjois 2016 (infections including infectious respiratory diseases).
Shi 2011 [39]	This study assessed the health care use and cost in 1 year after the lower respiratory tract infection (index events). This study was excluded because the duration (1 year after the index dates) was not suitable for this systematic review.
Yuan 2001 [19]	This study assessed the initial admissions with discharge diagnosis of infection. However, this study was excluded because the diagnosis of infection was not necessarily primary diagnosis.

Abbreviations: DCH = discharge home from the birth-hospitalization; NOS = Newcastle Ottawa Scale; SR = systematic review.

eTable 4: Other studies comparing all-cause admissions in infancy and early childhood

Study	Health service utilization	Effect estimates (95% confidence intervals)
Boyle 2012 [40]	≥ 3 admissions in DCH to 9 months ≥ 3 admissions in 9 months to 5 years	Adjusted OR = 5.1 (3.0, 8.8) Adjusted OR = 1.9 (1.3, 2.7)
Kato 2013 [41]	≥ 2 admissions in 6 months to 5.5 years	Adjusted OR = 1.6 (1.4, 1.9)*

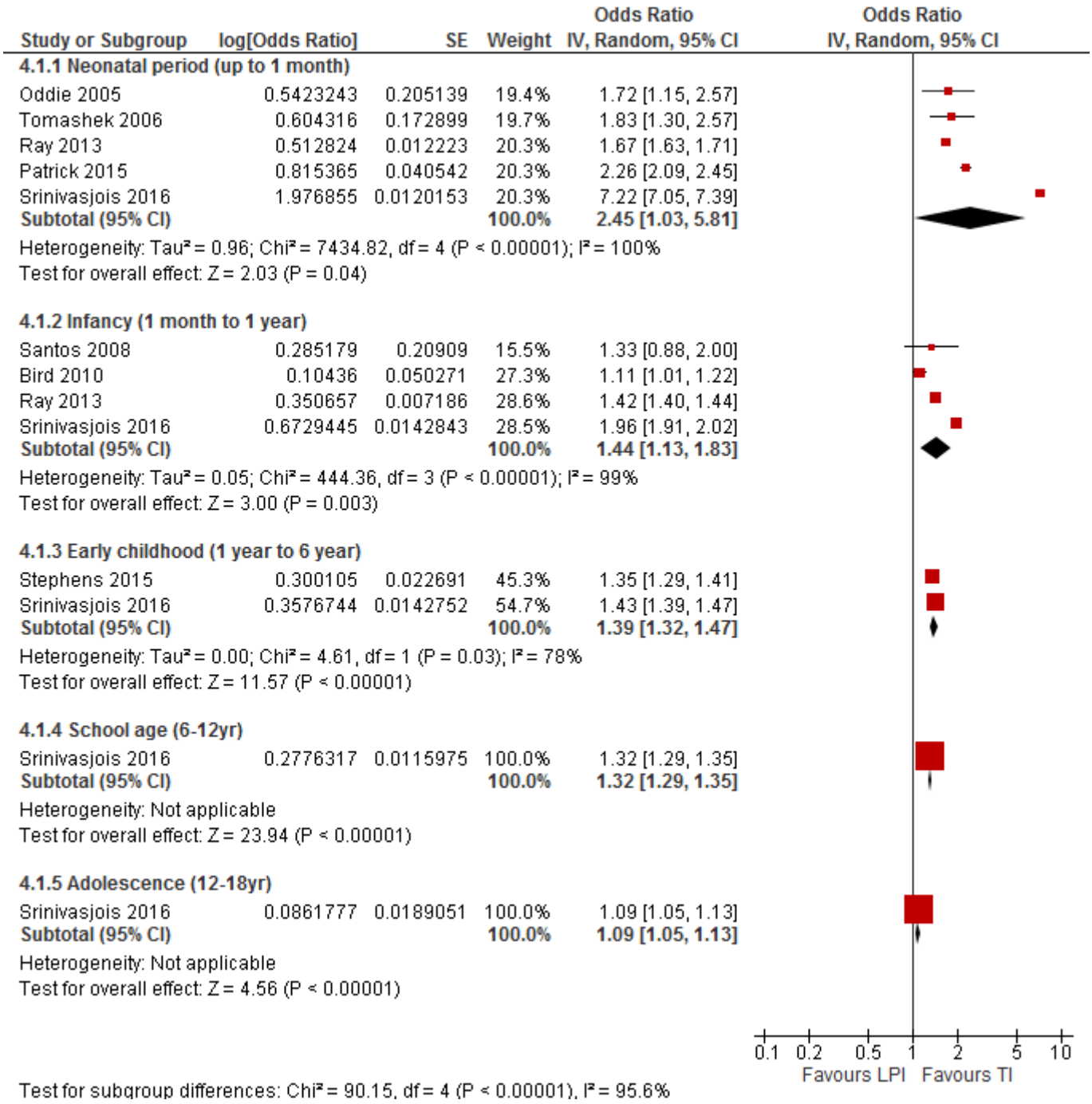
Abbreviations: DCH = discharge home from the initial birth hospitalizations; OR = odds ratios

eTable 5: Studies including special infant population

Study	Inclusion criteria	Health service utilization	Effect estimates (95% confidence intervals)
Celik 2013 [42]	Infants admitted to NICU	Admissions early after DCH	Crude OR = 2.7 (1.6, 4.7)
Escobar 1999 [43]	Infants admitted to NICU	Admissions within 14 days after DCH	Adjusted OR = 1.8 (1.3, 2.6)*
Kalyoncu 2010 [44]	Infants admitted to NICU	Admissions (> 24 hours) in DCH-2 months	Crude OR = 2.5 (1.1, 5.9)
Costello 2010 [45]	Infants with critical congenital heart disease	Admissions within 30 days after DCH	Crude OR = 0.7 (0.4, 1.4)

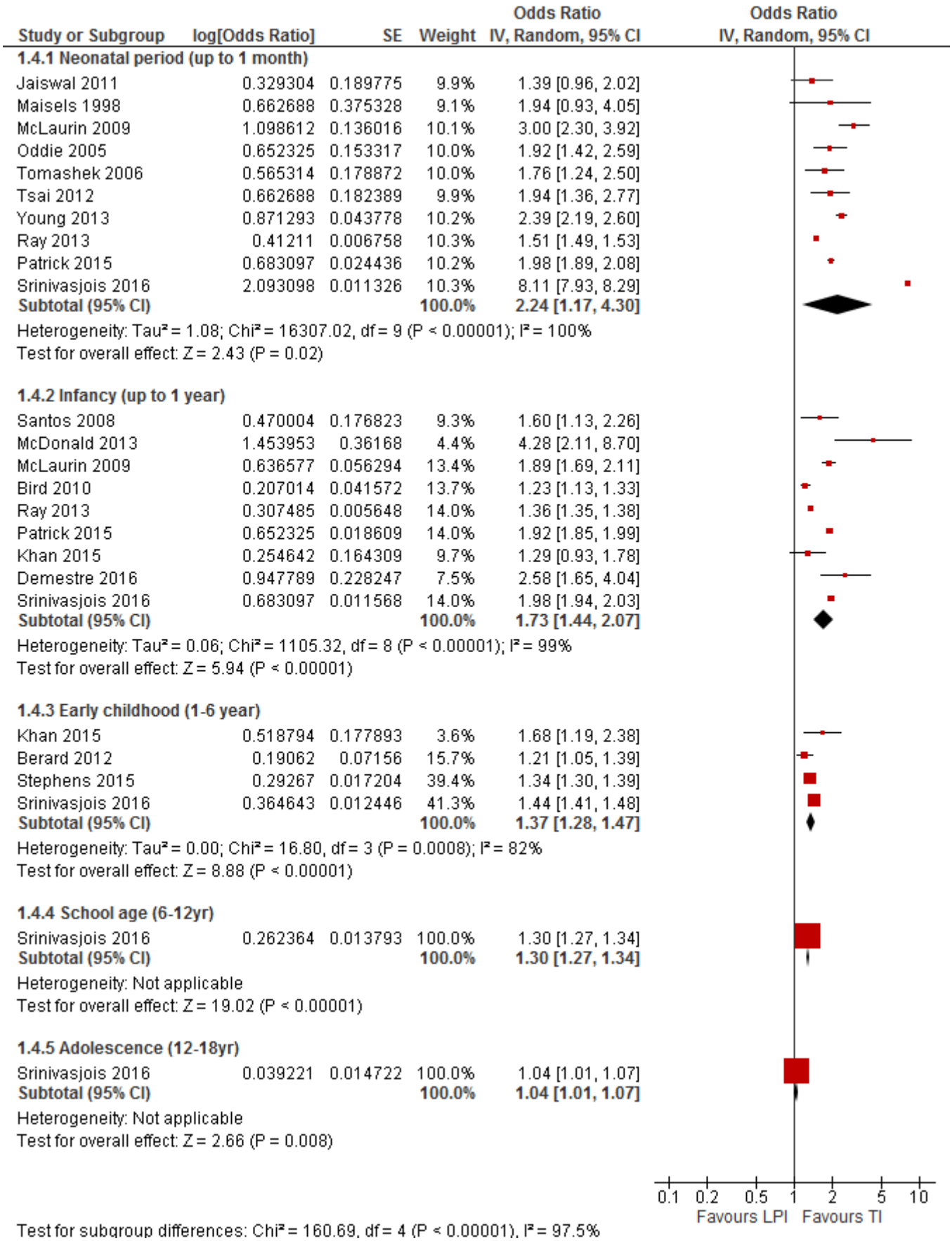
Abbreviations: DCH = discharge home from the initial birth hospitalizations; NICU = neonatal intensive care units; OR = odds ratios

eFigure 1: Sensitivity analysis including only high quality evidence of all-cause admissions of late preterm infants versus term infants from the neonatal period through adolescence



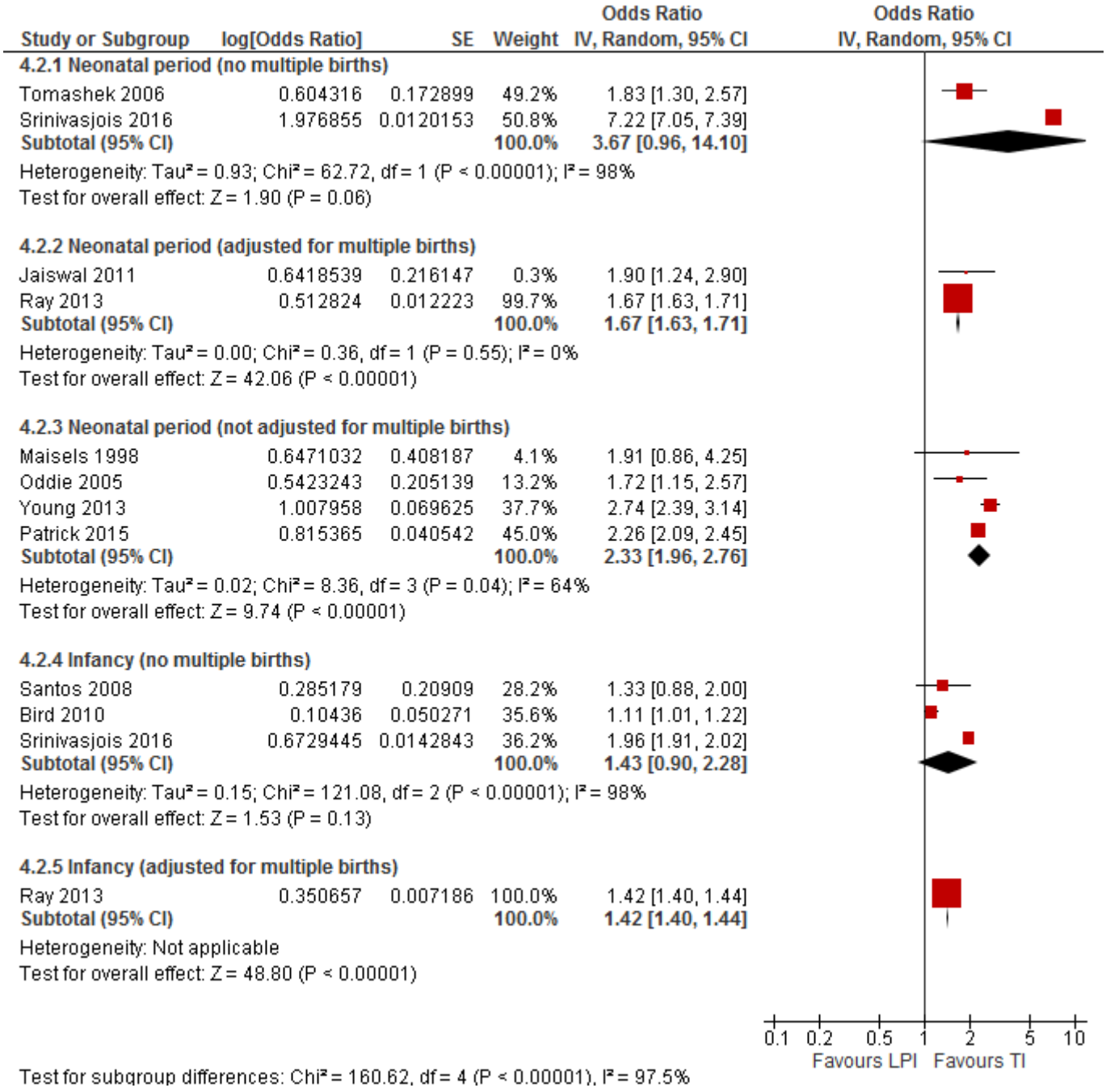
Abbreviations: LPI = late preterm infants; SE = standard errors; TI = term infants.

eFigure 2: Unadjusted odds ratios of all-cause admissions of late preterm infants versus term infants from the neonatal period through adolescence



Abbreviations: LPI = late preterm infants; SE = standard errors; TI = term infants.

eFigure 3: Odds ratios of all-cause admissions of late preterm infants versus term infants from the neonatal period through adolescence (Subgroup analysis stratified by adjustment for multiple births)



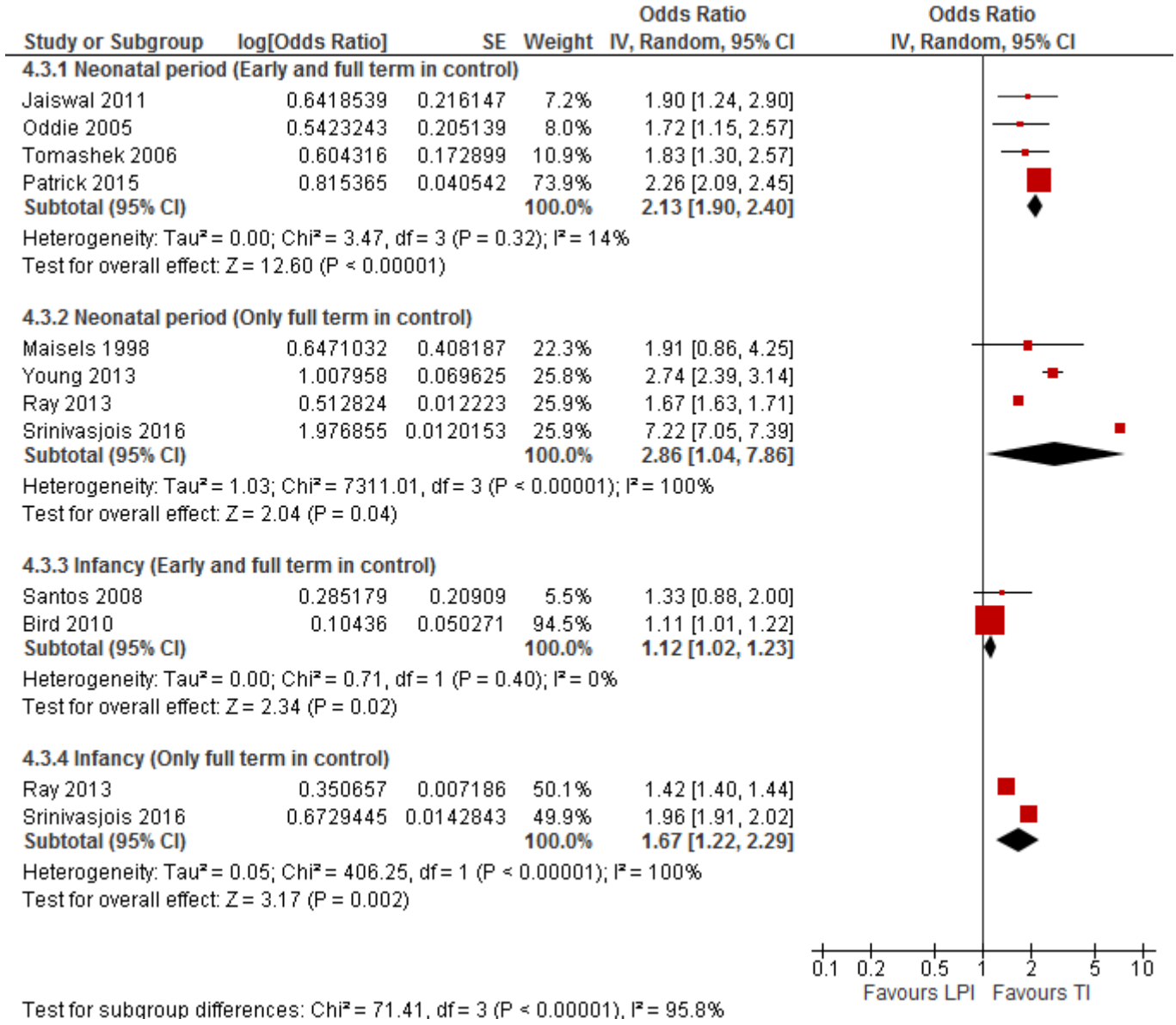
Test for subgroup differences

- *For the neonatal period: Chi² = 15.64, df = 2 (P < 0.001), I² = 87.2%*
- *For infancy: Test for subgroup differences: Chi² = 0.00, df = 1 (P = 0.97), I² = 0%*

The results from early childhood to adolescence were not presented here because all studies for the periods did not include multiple births.

Abbreviations: LPI = late preterm infants; SE = standard errors; TI = term infants.

eFigure 4: Odds ratios of all-cause admissions of late preterm infants versus term infants from the neonatal period through infancy (Subgroup analysis stratified by whether early term infants were included in the control)



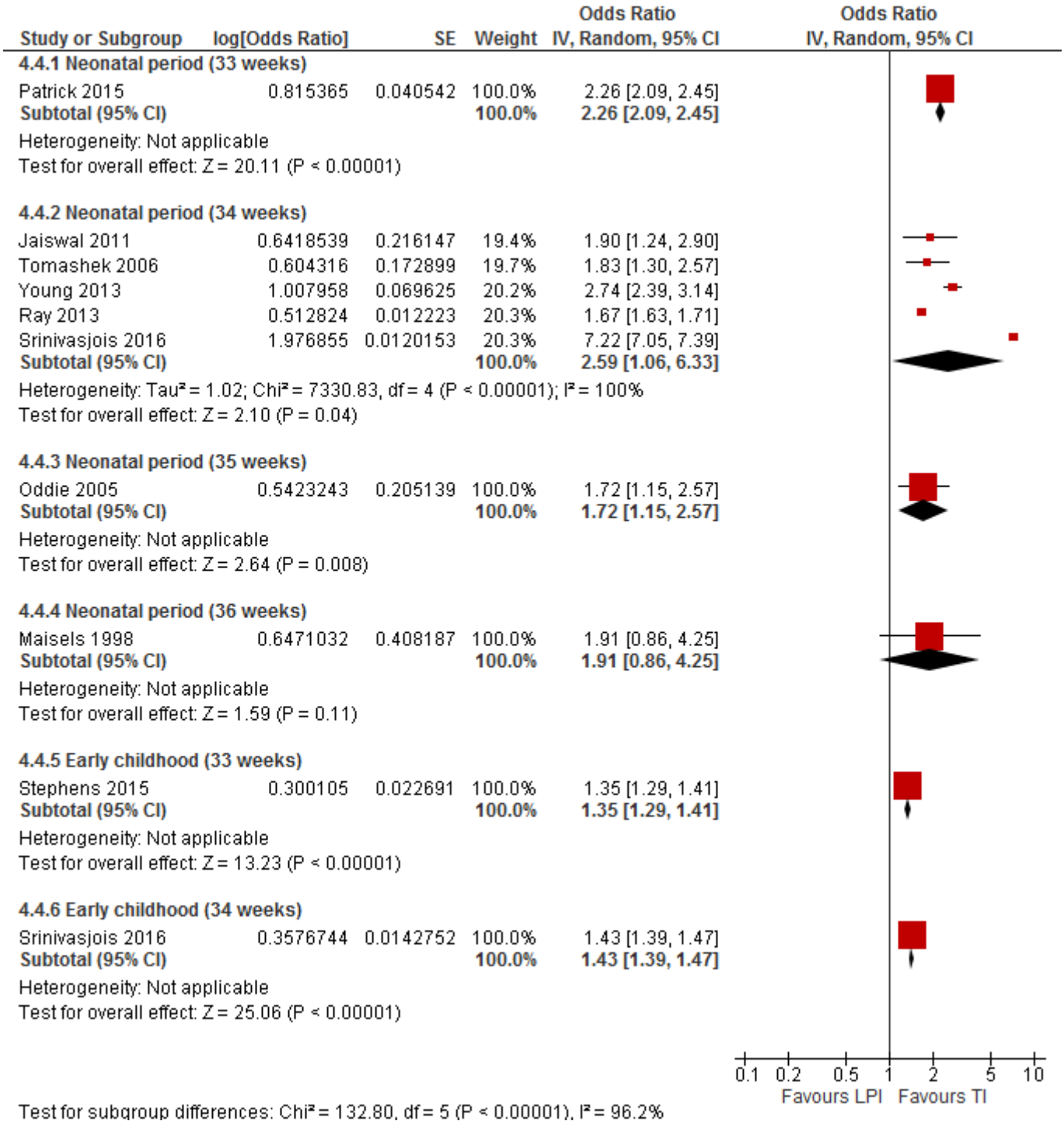
Test for subgroup differences

- *Neonatal period: Chi² = 0.32, df = 1 (P = 0.57), I² = 0%*
- *Infancy: Test for subgroup differences: Chi² = 5.57, df = 1 (P = 0.02), I² = 82.0%*

The results from early childhood to adolescence were not presented here because all studies for the periods included only full term infants in the control group.

Abbreviations: LPI = late preterm infants; SE = standard errors; TI = term infants.

eFigure 5: Odds ratios of all-cause admissions of late preterm infants versus term infants from the neonatal period through adolescence (Subgroup analysis stratified by the lower limit of gestational age of late preterm infants)



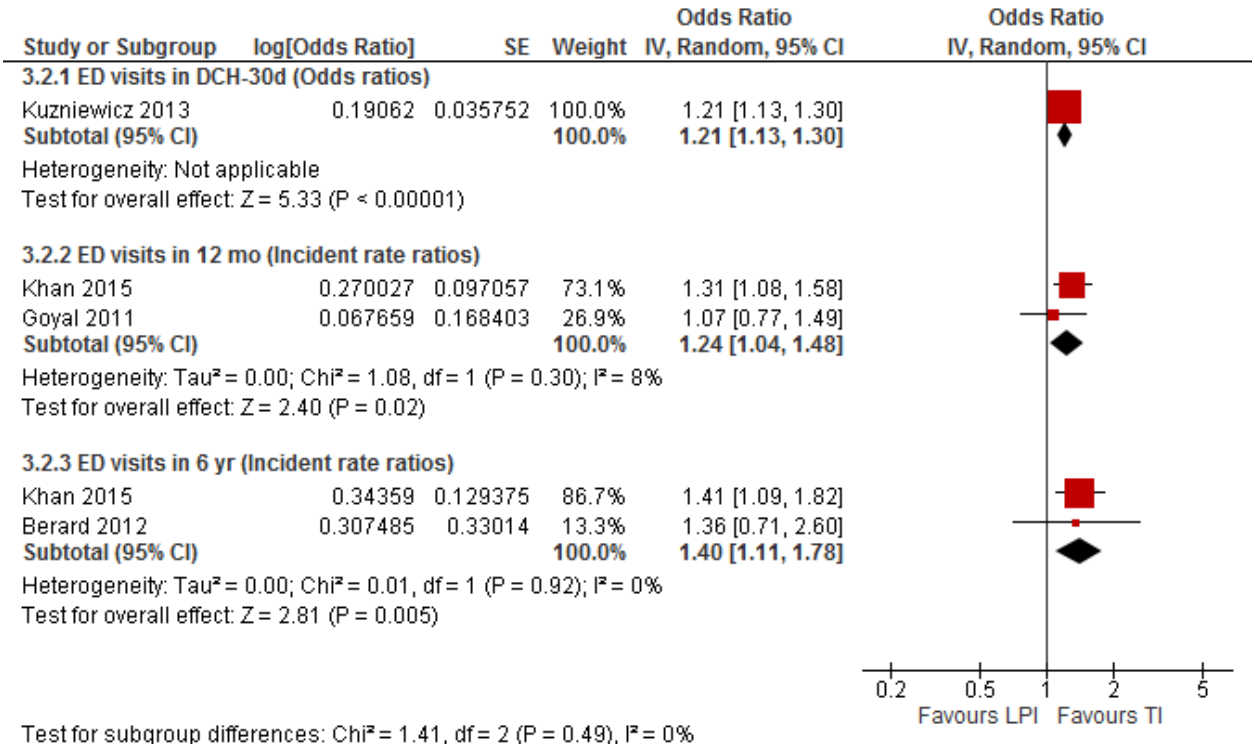
Test for subgroup differences

- *Neonatal period: Chi² = 1.96, df = 3 (P = 0.58), I² = 0%*
- *Early childhood: Test for subgroup differences: Chi² = 4.61, df = 1 (P = 0.03), I² = 78.3%*

The results for infancy, school age, and adolescence were not presented here because all studies for the periods included 34-36 weeks gestational age in late preterm infants.

Abbreviations: LPI = late preterm infants; SE = standard errors; TI = term infants.

eFigure 6: Unadjusted odds ratios of emergency department visits of late preterm versus term infants from the neonatal period to early childhood



Abbreviations: ED = emergency department; DCH = discharge home from the birth hospitalizations; LPI = late preterm infants; SE = standard errors; TI = term infants.

Supplemental References:

1. Flaherman VJ, Ragins AI, Li SX, Kipnis P, Masaquel A, Escobar GJ. Frequency, duration and predictors of bronchiolitis episodes of care among infants >/=32 weeks gestation in a large integrated healthcare system: a retrospective cohort study. *BMC Health Serv Res*. 2012;12:144.
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3. Escobar GJ, Masaquel AS, Li SX, Walsh EM, Kipnis P. Persistent recurring wheezing in the fifth year of life after laboratory-confirmed, medically attended respiratory syncytial virus infection in infancy. *BMC Pediatr*. 2013;13:97.
4. Kuzniewicz MW, Parker SJ, Schnake-Mahl A, Escobar GJ. Hospital readmissions and emergency department visits in moderate preterm, late preterm, and early term infants. *Clin Perinatol*. 2013;40(4):753-775.
5. Escobar GJ, Clark RH, Greene JD. Short-term outcomes of infants born at 35 and 36 weeks gestation: we need to ask more questions. *Semin Perinatol*. 2006;30(1):28-33.
6. Escobar GJ, Ragins A, Li SX, Prager L, Masaquel AS, Kipnis P. Recurrent wheezing in the third year of life among children born at 32 weeks' gestation or later: relationship to laboratory-confirmed, medically attended infection with respiratory syncytial virus during the first year of life. *Arch Pediatr Adolesc Med*. 2010;164(10):915-922.
7. Flaherman V, Li S, Ragins A, Masaquel A, Kipnis P, Escobar GJ. Respiratory syncytial virus testing during bronchiolitis episodes of care in an integrated health care delivery system: a retrospective cohort study. *Clin Ther*. 2010;32(13):2220-2229.
8. Burgos AE, Schmitt SK, Stevenson DK, Phibbs CS. Readmission for neonatal jaundice in California, 1991-2000: trends and implications. *Pediatrics*. 2008;121(4):e864-869.
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CAPTER 3

STUDY B

READMISSION AND EMERGENCY VISITS BY LATE PRETERM SINGLETONS AND TWINS IN THE FIRST 5 YEARS

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Readmission and emergency visits by late preterm singletons and twins in the first 5 years

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Abbreviations: aIRR: adjusted incidence rate ratio; aOR: adjusted odds ratios; DAD: Discharge Abstract Database; ED: emergency department; HSU: hospital service utilization(s); ICES: Institute for Clinical Evaluative Sciences

Table of Contents Summary: (25/25 words)
Hospital service use for the first 5 years was compared between late preterm singletons and twins with term infants in a population based cohort study.

What's Known on This Subject
Late preterm infants, compared with term infants, have higher risks of mortality and morbidity and higher rates of re-admissions especially during the neonatal period.

What This Study Adds

Late preterm infants had more frequent admissions and emergency department visits than term infants in both singletons and twins through 5 years of age. The difference in admissions between late preterm and term infants was smaller in twins than singletons.

Contributor's Statement:

Dr Isayama conceptualized and designed the study, developed the study protocol, obtained the approval for data access, conducted the analyses, interpreted the study results, wrote the first draft manuscript, and revised the manuscript. Dr. Isayama had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Drs O'Reilly and Beyene provided advice for designing the study, developing the study protocol, and conducting the analyses, interpreted the study results, and critically reviewed and revised the manuscript.

Drs Shah, Lee, and Guttmann provided advice for developing the study protocol, and critically reviewed and revised the manuscript.

Dr McDonald supervised all aspects of this study, conceptualized and designed the study, developed the protocol, provided advice for conducting the analyses, interpreted the study results, and critically reviewed and revised the manuscript.

All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work**.**

Abstract:

Objectives: To compare re-admissions and emergency department (ED) visits of late preterm singletons and twins versus term infants in the first 5 years.

Methods: This is a population-based cohort study using health administrative data including singletons and twins born alive at 34-41 weeks gestation in Ontario, Canada, from 2002 to 2012 who survived at initial discharge. The incidence rates of admissions and ED visits from discharge home after birth to 5 years of age (discharge to 28 days; 29 days to 1 year; 1 to 5 years of age) were compared between late preterm and term infants using negative binomial regression analyses with generalized estimating equations, stratified by twins and adjusted for maternal and infants' characteristics.

Results: A total of 1,316,931 infants (75,364 late preterm and 1,241,567 term infants) were included. Late preterm infants had more frequent admissions than term infants in the first 5 years in both singletons (6 vs. 4 admissions per-1000-person-month, adjusted incidence rate ratio [aIRR] 1.46 [95% confidence interval 1.42-1.49]) and twins (5 vs. 4 admissions per-1000-person-month, aIRR 1.21 [1.11-1.31]). The aIRR for admissions was largest in the first 28 days after birth (aIRR 2.21 [2.13-2.29] in singletons; aIRR 1.40 [1.18-1.66] in twins) and decreased with the children's ages. The similar increased frequency in late preterm versus term infants were found for ED visits in all the periods.

Conclusions: Late preterm infants had more frequent admissions and ED visits than term infants in both singletons and twins through 5 years of age.

INTRODUCTION

Late preterm births, defined as those at 34 to 36 completed weeks of gestation, make up 6% of singleton live-births and 40% of twin live-births.[1] Compared to term infants, growing evidence identifies that late preterm infants have significantly higher risks of mortality and both short- and long–term morbidity, including respiratory distress, hypoglycemia, thermal instability, jaundice requiring phototherapy, feeding problems, and apnea, poor growth, neurodevelopmental impairment, behavioral or psychiatric problems.[2-5] Although the adverse outcomes of late preterm infants are less severe than those of earlier preterm infants, the total impact on the population and health system is significant because late preterm infants make up approximately three fourths of preterm infants.[1]

The increased morbidity results in higher rates of admissions to neonatal intensive care units during initial birth hospitalizations[5] and re-admissions and emergency department (ED) visits during the neonatal period.[6-8] However, the information on admissions and ED visits is limited on longer follow-up, especially after 1 year of age. In addition, most previous studies have not evaluated or stratified by multiple births (mostly twins). The

consideration of multiple births is important in assessing late preterm infants because the proportion of twins is much higher in late preterm infants (15%) than term infants (1.5%).[1] Because multiple births have increased risks of mortality and morbidity,[9] the increased admission or ED visits in late preterm infants might be additively or multiplicatively larger in twins than singletons.

Hence, this study evaluated admissions and ED visits after initial discharge home up to 5 years of age in late preterm versus term infants (singletons and twins) in Ontario, Canada with a publicly funded universal health insurance system.

METHODS

This is a retrospective population-based cohort study including all live-born singletons and twins born at 34 to 41 weeks gestation between 2002 and 2012 in Ontario, Canada, who survived at initial discharge home after birth hospitalizations. Ontario is the most populous Canadian province with over 13 million people and approximately 140,000 live births per year.[10]

Data sources: The existing linked administrative databases at the Institute for Clinical Evaluative Sciences (ICES) in Ontario were used.[11, 12] The quality of

coding the ICES database data were evaluated by data re-abstraction studies[13-15] and the ICES data have previously been used to study health outcomes and health services.[16-18] The data on maternal delivery (gestational age at delivery, maternal comorbidities, mode of delivery, multiple births, etc.), and infants' hospital admissions (dates of admissions and discharge, primary causes for admissions, other diagnoses during hospital stays, lengths of hospital stays, transfer to another hospital) were derived from the Discharge Abstract Database (DAD) containing the data of all inpatient hospitalizations in Ontario. Gestational age at delivery recorded in the DAD was based on the best clinical estimation by attending physicians (mostly estimated by fetal ultrasound or if unavailable last menstrual period) or documentation of nursing staff as a secondary source.[19] Between-hospital transfers without discharge home were considered one admission. The mother-newborn pairs were identified using the MOMBABY database in which the DAD data of mothers and their newborns born in the fiscal year 2002 onward were deterministically linked based on chart number.[16] The National Ambulatory Care Reporting System was used for the data on ED visits (visit dates, primary causes for the visits).[15] The primary cause for each admission or ED visit was defined as the

diagnosis that was considered most responsible for the hospital stay or visits contributing to the greatest proportion of the stay or the greatest resource use at the hospital. The Registered Persons Database was used for the information of demographics, registration in the Ontario Health Insurance Plan, and deaths of participants. These multiple databases were linked in the ICES databases using unique anonymized encrypted identifiers. The diagnostic data in these ICES databases use the International Statistical Classification of Diseases and Related Health Problems, 10th Revision Canada and Canadian Classification of Health Interventions (eTables 1 and 2 in the supplement). We excluded infants who died before initial discharge home, who had congenital anomalies or chromosomal abnormalities, higher-order multiple births (i.e. triplets or more), and those born out of hospitals (e.g. home births less than 3% of all births in Ontario).[20]

Comparisons: Late preterm infants born at 34-36 weeks gestation were compared with term infants born at 37-41 weeks gestation. Potential confounders included maternal characteristics (maternal age [≤18, 19-27, 28-36, ≥37 years of age], multi-gravida, preeclampsia or eclampsia, gestational diabetes, premature rupture of membranes, placental abruption, caesarean

section, oxytocin use, neighborhood income) and infants' characteristics (twin status, sex, small for gestational age [< 10 percentile], neonatal care levels of birth hospitals, and infants' complications during birth hospitalizations including hypoglycemia, jaundice, feeding or gastrointestinal problems, cardio-respiratory problems, neurological problems or asphyxia, sepsis). The maternal neighborhood income was categorized into low (the lowest quintile), medium (the second to fourth quintiles), and high level (the highest quintile) based on maternal postal code using Statistics Canada census data.[21] The birth hospitals' level of newborn-care was defined according to the provincial designation as: level 1 (basic care), level 2 (moderately advanced care), or level 3 (highly advanced care).[22]

Primary and secondary outcomes: The primary outcomes were hospital admission rates from the initial discharge home after birth up to 5 years of age as well as those in 3 specific periods: from the initial discharge home after birth hospitalizations to 28 days of age, from 29 days to 1 year of age, and from 1 to 5 years of age. The secondary outcomes included ED visit rates and length-of-stays of hospital admissions.

Analyses: Maternal and infant characteristics were compared between late preterm and term infants using Chi-square tests. The rates of admissions and ED visits were calculated per 1000 person-month (month = 30 days) and compared between late preterm and term infants using negative binomial regression analyses adjusting for maternal and infant characteristics (primary analyses). The analyses were stratified into singletons and twins due to significant interactions in most of the comparisons. The results are presented as adjusted incidence rate ratios (aIRR) of admissions and ED visits. A generalized estimating equation was used to accommodate the inter-cluster correlation among twins and among infants born to the same mothers (i.e. siblings). Because some infants were lost to follow up before 5 years of age due to death or moving out of Ontario, the length of follow-up period for each child was calculated from the ICES data of patients' enrollment in the Ontario Health Insurance Plan in quarter-year intervals and was used to calculate the rates of admissions and ED visits in the analyses. Z tests were used to compare the aIRR between singletons and twins and between admissions and ED visits. The length-of-stay per admissions was compared between late preterm and term infants who had at least one admission during the periods of interest

using linear regression analyses after log-transformation of the length-of-stay. The log-transformation was used because the length-of-stay had a right-skewed distribution. The results were presented as the percent changes in the geometric means of length-of-stay of late preterm infants compared with term infants. The proportions of the primary causes for admissions and ED visits are presented as 100% stacked column charts. For the primary analysis comparing admission rates in 4 periods by singletons or twins (a total of 8 outcomes), the statistical significance was judged based on two-sided α-levels calculated using the step-down Bonferroni correction.[23] The α-level for the n^{th} lowest P-value (n= 1 to 8) was given by the following.

$$\alpha\ level = 0.05 \div (9 - n)$$

For example, the α-levels were 0.0063 (=0.05÷8) for the lowest p-value (n=1) and 0.0072 (=0.05÷7) for the second lowest p-value (n=2). For other analyses, the two-sided α-level of 0.05 was used. All of the analyses were conducted using SAS 9.3.

Ethics and sample size: This study was approved by the Research Ethics Board at McMaster University. The sample size of this study was decided based on the availability of the ICES data using ICD 10^{th} codes when the study

was planned. Based on the actual sample size of this study, the power of the analysis to find at least one significant difference in admissions between late preterm and term infants was 0.76 for IRR 1.10, 0.89 for IRR 1.15, and 0.94 for IRR 1.20 using the lowest α-level of 0.00625 for the step-down Bonferroni correction.

RESULTS

Population and characteristics

Among 1,388,011 singletons or twins born alive at 34-41 weeks gestation in hospitals in Ontario from 2002 to 2012, 1,323,158 infants were eligible excluding infants who had congenital anomalies or chromosomal abnormalities or died during the birth hospitalization. After excluding infants who had missing data on the lengths of stay for birth hospitalizations (2 infants), maternal neighborhood income (6163 infants), or birth weight (62 infants), this study included 1,316,931 infants with 75,364 late preterm infants (6%) and 1,241,567 term infants (94%). All of the maternal and infant characteristics were significantly different between late preterm and term infants (Table 1). In particular, late preterm infants compared with term infants

were more likely to: be born to mothers with preeclampsia or eclampsia (6% versus 1%) or premature rupture of membrane (30% versus 8%), be born by caesarian section (40 versus 27%) and be twins (22% versus 2%).

Admissions and ED visits in late preterm versus term infants

Late preterm infants had significantly more frequent admissions than term infants, in both singletons (6 versus 4 admissions per 1000 person-month, aIRR 1.46 [95% confidence interval 1.42-1.49]) and twins (5 versus 4 admissions per 1000 person-month, aIRR 1.21 [1.11-1.31]) after the initial discharge to 5 years of age overall, as well as in all of the individual time periods (Figures 1A and 2A). The difference between late preterm and term infants decreased with the children's age. In addition, the aIRR estimates were significantly smaller for twins than singletons ($P<0.001$) except for the period from 1 to 5 years (eTable 3). As with admissions, ED visits were more frequent in late preterm singletons (64 versus 57 ED visits per 1000 person-month, aIRR 1.14 [1.12-1.15]) and twins (49 versus 41 ED visits per 1000 person-month, aIRR 1.15 [1.11-1.19]) than term infants (Figures 1B and 2B), although the difference between late preterm and term infants was marginal for ED visits compared with those for admissions of singletons (eTable 4).

Although the length-of-stay per admissions among infants who had at least one admission was slightly different between late preterm and term singletons in some periods, the differences were minimal (the percent change in the length-of-stay < 10%, Table 2).

Primary causes for admissions and ED visits

During the neonatal period, jaundice was the most common primary diagnosis for admission for both late preterm and term infants (Figure 3). After the neonatal period, in both late preterm and term infants, the most common primary cause for admissions were respiratory tract diseases, mainly lower tract problems, followed by feeding or gastrointestinal problems or infection. For ED visits, during the neonatal period, jaundice, respiratory problems, and feeding or gastrointestinal problems were the top 3 common primary causes in both late preterm and term infants. From infancy onward, respiratory tract diseases, mainly upper respiratory tract diseases, were the most common reason for ED visits in both late preterm and term infants. Notably, injuries increased after 1 year of age from 7-9% to 19-22% and were the second most common primary cause for ED visits in both late preterm and term infants.

DISCUSSION

This population-based cohort study including 1.3 million infants found that late preterm infants compared with term infants had higher rates for admissions and ED visits after initial discharge up to 5 years of age, although the rate differences decreased as the children got older. To our knowledge, this study is the first study to identify that the increased frequency of admissions of late preterm infants compared with term infants was smaller in twins than singletons, although still present. The increased frequency of late preterm versus term infants were also present for ED visits, although smaller than for admissions of singletons.

Previous studies reported that late preterm infants had more re-admissions than term infants in the neonatal period; however, the information was limited after that, especially after 1 year of age. [7, 8, 24, 25] A South Carolina cohort study using Medicaid data reported the increased re-admission rates of late preterm infants than term infants after birth hospitalizations to 6 years of age (aIRR = 1.39 [1.22-1.56]).[26] A national survey in the UK with a 67% response rate reported that late preterm infants had higher odds of having 3 or more admissions from 9 months to 5 years of age compared with full term

infants of 39-41 weeks gestational age (4.9% versus 2.8%; adjusted odds ratio [aOR] = 1.9 [1.3-2.7]).[27] A population-based cohort study of singletons in New South Wales, Australia, reported that infants at 35-36 weeks gestational age had a higher odds of having 2 or more admissions from 1 to 6 years of age than full term infants of 39-40 weeks (aOR = 1.36 [1.29-1.44]).[28] Another population-based cohort study of singletons in West Australia reported the increased re-admissions up to 18 years of age in late preterm infants compared with full term infants of ≥ 39 weeks gestational age (aIRR = 2.10 [2.04-2.15] from 29 days to 1 year, 1.49 [1.46-1.52] from 1 to 5 years, 1.33 [1.30-1.36] from 5 to 12 years, and 1.14 [1.11-1.18] from 12 to 18 years).[29] Although our findings were in line with these of increased admissions of late preterm infants even after 1 year of age, these previous studies included only singleton data or analyzed singletons and twins together without stratification.

Unlike our study, previous reports found no significant difference in ED visits between late preterm and term infants, although there were fewer studies than for admissions for comparison. A cohort study in California reported that the rate of ED visits within 30 days after discharge from birth hospitalizations of late preterm infants were not significantly different from

those of infants of ≥ 39 weeks gestational age (4.7% versus 3.9%; aOR 1.08[1.00-1.17]).[8] A cohort study in South Carolina found no significant difference in the ED visits between late preterm and term infants after birth hospitalization to 6 years of age (aIRR = 1.01 [0.96-1.05]).[26] The discrepancy between our study's results of higher ED visits and the previous studies was not clear and it may be related to the difference in the health care systems studied.

The most common cause for re-admissions in the neonatal period was jaundice in our study but varied among previous studies including feeding problems and infection as well as jaundice.[7, 8, 25] The variation may be due to discharge criteria of the initial birth hospitalizations because longer stay during the birth hospitalization likely decreases the re-admission or ED visits due to jaundice and feeding problems, but is a topic that requires further studies. After the neonatal period, common causes for admission in a population-based cohort study from Western Australia were infection in all the periods up to 12 years of age.[30] Although this was different from our study finding that the most common causes for admissions after the neonatal period were respiratory tract diseases, it is likely due to the difference in the

categorization of the diagnoses, with infections of the respiratory tract (e.g. bronchiolitis, bronchitis) categorized as infection in the previous study and as respiratory tract diseases in ours.

Several strengths of our study include, firstly, the use of a large population-based cohort of infants using administrative database for which the quality of data coding is assessed and reported.[13-15] Second, the adjustment for various potential confounders including maternal, infant and socioeconomic factors provided independent effect estimates of late preterm birth on admissions and ED visits. Third, the analyses stratified into twins and singletons shed light on another aspect on these hospital service utilizations as the difference in admission rates between late preterm and term infants was larger in singletons than twins. Fourth, the inter-cluster correlation among twins and siblings were accommodated in the analyses by a generalized estimating equation.

There were some limitations of this study. Because the ICES database did not capture births out of hospitals (e.g. home births), the small proportion of infant population was not included in this study. In addition, although the loss-to-follow-up due to deaths or moving out of the province was

incorporated in the analyses, it was previously reported that the ICES database underestimates the number of death as well as people moving out of province causing overestimating the lengths of follow-up in this study.[31] Health care in Canada is provided by a publicly funded universal health care system, and the admissions and ED visits are free for all infants born in Canada. Therefore, the results of this study may not be generalizable to other health care systems. In addition, other differences in health care provision to mothers and newborns may affect the admissions and ED visits including hospital policies of length of hospital stay after birth,[32] early post-discharge follow up programs, early home visits policies,[33] and availability of pediatric observational units.[34]

Implications of our findings that both late preterm singletons and twins have higher rates than term infants of admissions and ED visits to 5 years of age may include a need to provide targeted parental education on breastfeeding and healthy habits for preventing infections, close post-discharge follow-up, and encouragement of vaccinations for late preterm infants. The increase in admissions in late preterm versus term infants was smaller in twins than singletons in contrast to our study hypothesis. It was not

clear the reasons for this and further studies are needed to investigate this point.

CONCLUSION

After adjusting for covariates, late preterm infants had more frequent admissions and ED visits after initial birth hospitalisation throughout the study period of the first 5 years of age. The rate difference in admissions between late preterm and term infants was significantly smaller in twins than singletons, although still present. Administrators, care providers and families of late preterm infants need to be made aware of these long-term increases in admissions and ED visits.

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Figures and legends

Figure 1: Admissions and ED visits of late preterm versus term infants in a population-based cohort study of late preterm singletons and twins admissions and ED visits during the first 5 years of life: A) Admission rates (per 1000 person-month), B) ED visits rates (per 1000 person-month).
Figure 1 legend: The numbers in the figures were presented by *per 1000 person-month (month = 30 days)*. The difference in hospital service utilization between late preterm and term infants were all significant for all (See Figure 2 for the detail). Abbreviations: P1 = period 1 after discharge home from birth hospitalizations to 28 days of age; P2 = period 2 from 29 days to 1 year of age; P3 = period 3 from 1 to 5 years of age.

Figure 2: Adjusted comparisons of admissions and ED visits of late preterm versus term infants in a population-based cohort study of late preterm singletons and twins admissions and ED visits during the first 5 years of life: A) Admissions (primary outcome), B) Emergency department visits
Figure 2 legend: Abbreviations: 95%CI = 95% confidence intervals; d = days; DCH = discharge home after birth hospitalizations; ED = emergency department; aIRR = adjusted incidence rate ratios; LPI = late preterm infants; TI = term infants; yr = year(s).
The sIRR were estimated using negative binomial regression with generalized estimating equation adjusting for maternal or delivery factors (maternal age, gravida, pre-eclampsia or eclampsia, diabetes, premature rupture of membrane, placental abruption, Caesarean section, oxytocin use, and neighborhood income), infant factors (sex, small for gestational age, neonatal care levels of birth hospitals), and neonatal complications during birth hospitalizations (hypoglycemia, jaundice, cardio-respiratory problems, neurological problems, feeding or gastrointestinal problems, sepsis).

Figure 3: Primary causes for admissions and ED visits in a population-based cohort study of late preterm singletons and twins admissions and ED visits during the first 5 years of life
Figure 3 legend: Abbreviations: ED = emergency department; GI problems = gastrointestinal problems; LPI = late preterm infants; P1 = period 1 after discharge home from birth hospitalizations to 28 days of age; P2 = period 2 from 29 days to 1 year of age; P3 = period 3 from 1 to 5 years of age; TI = term infants.

Table 1: Maternal and neonatal characteristics in a population-based cohort study of late preterm singletons and twins' admissions and ED visits during the first 5 years of life

			Late preterm infants (N=75364)		Term infants (N=1241567)		Chi^2 P values
Maternal or delivery factors	**Maternal age**	**1: ≤ 18 yr**	1,632	2%	25,564	2%	<.0001
		2: 19-27 yr	20,789	28%	367,756	30%	
		3: 28-36 yr	42,264	56%	706,797	57%	
		4: ≥ 37 yr	10,679	14%	141,450	11%	
	Gravida ≥ 1		48,580	64%	835,398	67%	<.0001
	Preeclampsia/ Eclampsia		4,700	6%	8,860	1%	<.0001
	Maternal Diabetes melitus		6,718	9%	58,330	5%	<.0001
	PROM		22,975	30%	101,308	8%	<.0001
	Abruptio placenta		2,665	4%	7,642	1%	<.0001
	Oxytocin use		18,790	25%	343,720	28%	<.0001
	Caesarean section		29,980	40%	334,474	27%	<.0001
	Maternal income	**1: low**	16,994	23%	277,102	22%	0.03
		2: middle	46,098	61%	757,843	61%	
		3: high	12,272	16%	206,622	17%	
Infant factors	**Twin**		16,575	22%	20,301	2%	<.0001
	Male sex		40,263	53%	628,883	51%	<.0001
	SGA		4,322	6%	60,381	5%	
	Neonatal care level of birth hospitals	**level 1**	7,745	10%	183,149	15%	<.0001
		level 2	52,932	70%	876,618	71%	
		level 3	14,687	19%	181,800	15%	
Infants' complications during birth hospitalizations	**Hypoglycemia**		10,108	13%	35,384	3%	<.0001
	Jaundice		21,984	29%	64,648	5%	<.0001
	Feeding/GI problems		11,439	15%	20,699	2%	<.0001
	Cardio-respiratory problems		18,732	25%	76,392	6%	<.0001
	Neurological problems		912	1%	8,142	1%	<.0001
	Sepsis		2,319	3%	7,642	1%	<.0001

Abbreviations: GI problems = gastrointestinal problems; LPI = late preterm infants; PROM = premature rupture of membrane; SGA = small for gestational age (< 10 percentile); TI = term infants; yr = years.

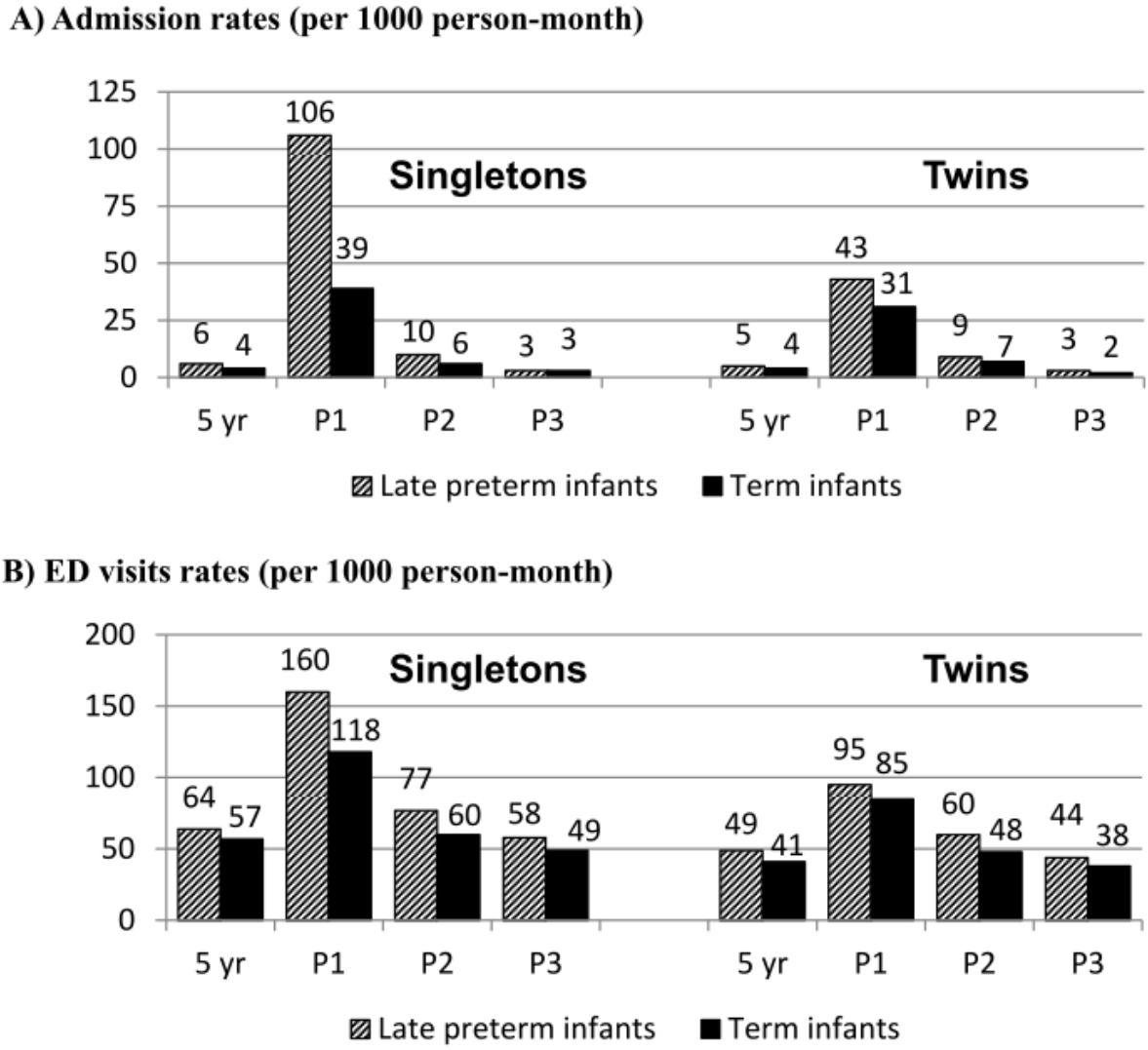
Table 2: Adjusted comparisons of length of stay of late preterm versus term infants in a population-based cohort study of late preterm singletons and twins' admissions and ED visits during the first 5 years of life

	N of infants admitted (%)		Median of LOS (Q1-Q3)		Geometric means of LOS days (95% CL)		Δ%LOS* (95%CI)	P values
	LPI	TI	LPI	TI	LPI	TI		
Singletons								
All 5 yr	13,222 (22%)	174,003 (14%)	2 (1-3)	2 (1-3)	2.0 (2.0-2.0)	1.9 (1.9-1.9)	2% (0% ,3%)	0.02
DCH-28d	4,341 (7%)	38,841 (3%)	2 (1-2)	2 (1-3)	1.8 (1.8-1.9)	1.9 (1.9-1.9)	-5% (-7% ,-3%)	<.0001
29d-1yr	4,979 (9%)	62,191 (5%)	2 (1-4)	2 (1-3)	2.3 (2.3-2.4)	2.2 (2.2-2.2)	2% (-1% ,4%)	0.15
1-5yr	5,710 (10%)	90,167 (7%)	2 (1-3)	2 (1-3)	1.8 (1.8-1.9)	1.8 (1.8-1.8)	2% (0% ,4%)	0.02
Twins								
All 5 yr	2,871 (17%)	2,904 (14%)	2 (1-3)	2 (1-3)	2.2 (2.1-2.2)	2.1 (2.0-2.1)	4% (0% ,9%)	0.06
DCH-28d	447 (3%)	492 (2%)	2 (1-5)	2 (1-4)	2.4 (2.2-2.6)	2.4 (2.2-2.6)	2% (-11% ,17%)	0.78
29d-1yr	1,349 (8%)	1,225 (6%)	2 (1-4)	2 (1-4)	2.5 (2.4-2.6)	2.4 (2.3-2.5)	4% (-3% ,11%)	0.24
1-5yr	1,389 (8%)	1,486 (7%)	2 (1-3)	2 (1-3)	1.8 (1.7-1.8)	1.8 (1.7-1.8)	1% (-4% ,7%)	0.60

Abbreviations: d = days; DCH = discharge home after birth hospitalizations LOS = length of stay (days); LPI = late preterm infants; Q1 = quartile 1; Q3 = quartile 3; TI = term infants; yr = years.

*****Δ%LOS (95%CI) indicated the percentage changes of the geometric mean of length of hospital stay of late preterm infants compared with term infants. For example, Δ%LOS (95%CI) = 2% indicated that the geometric mean of length of stay of late preterm infants were 2% longer than that of term infants (e.g. 2.0 days versus 1.9 days). The negative Δ%LOS meant that the LOS was shorter in late preterm infants than term infants. The Δ%LOS and P values were estimated using linear regression with generalized estimating equation for log-transformed LOS adjusting for maternal or delivery factors (maternal age, gravida, pre-eclampsia or eclampsia, diabetes, premature rupture of membrane, placental abruption, Caesarean section, oxytocin use, and neighborhood income), infant factors (sex, small for gestational age, neonatal care levels of birth hospitals), and neonatal complications during birth hospitalizations (hypoglycemia, jaundice, cardio-respiratory problems, neurological problems, feeding or gastrointestinal problems, sepsis).

Figure 1: Admissions and ED visits of late preterm versus term infants in a population-based cohort study of late preterm singletons and twins admissions and ED visits during the first 5 years of life



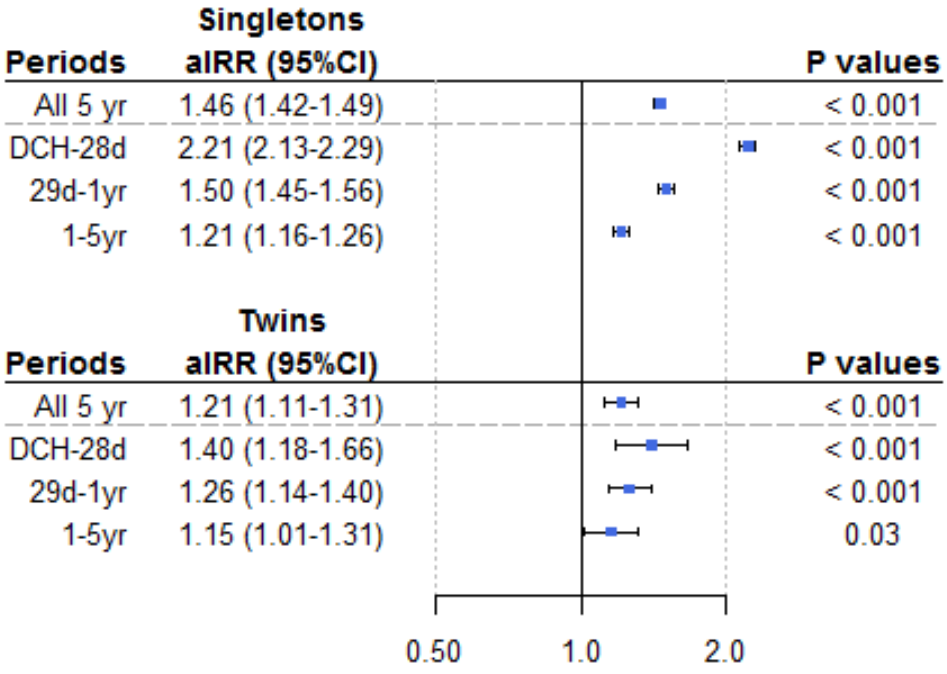
The numbers in the figures were presented by *per 1000 person-month (month = 30 days)*.

The difference in hospital service utilization between late preterm and term infants were all significant for all (See Figure 2 for the detail).

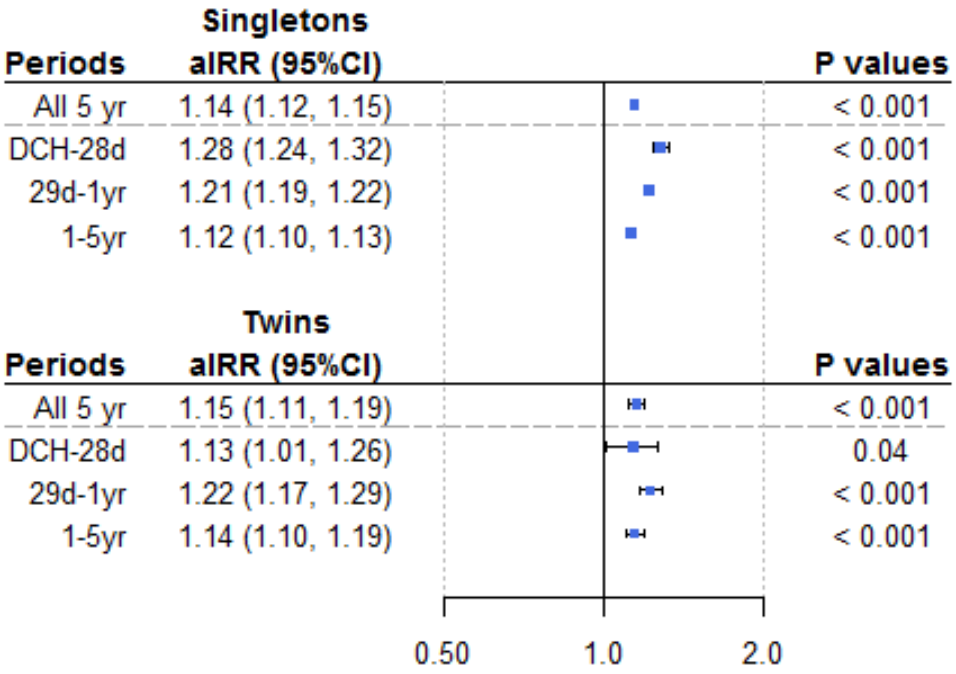
Abbreviations: P1 = period 1 after discharge home from birth hospitalizations to 28 days of age; P2 = period 2 from 29 days to 1 year of age; P3 = period 3 from 1 to 5 years of age.

Figure 2: Adjusted comparisons of admissions and ED visits of late preterm versus term infants in a population-based cohort study of late preterm singletons and twins admissions and ED visits during the first 5 years of life

A) Admissions (primary outcome)



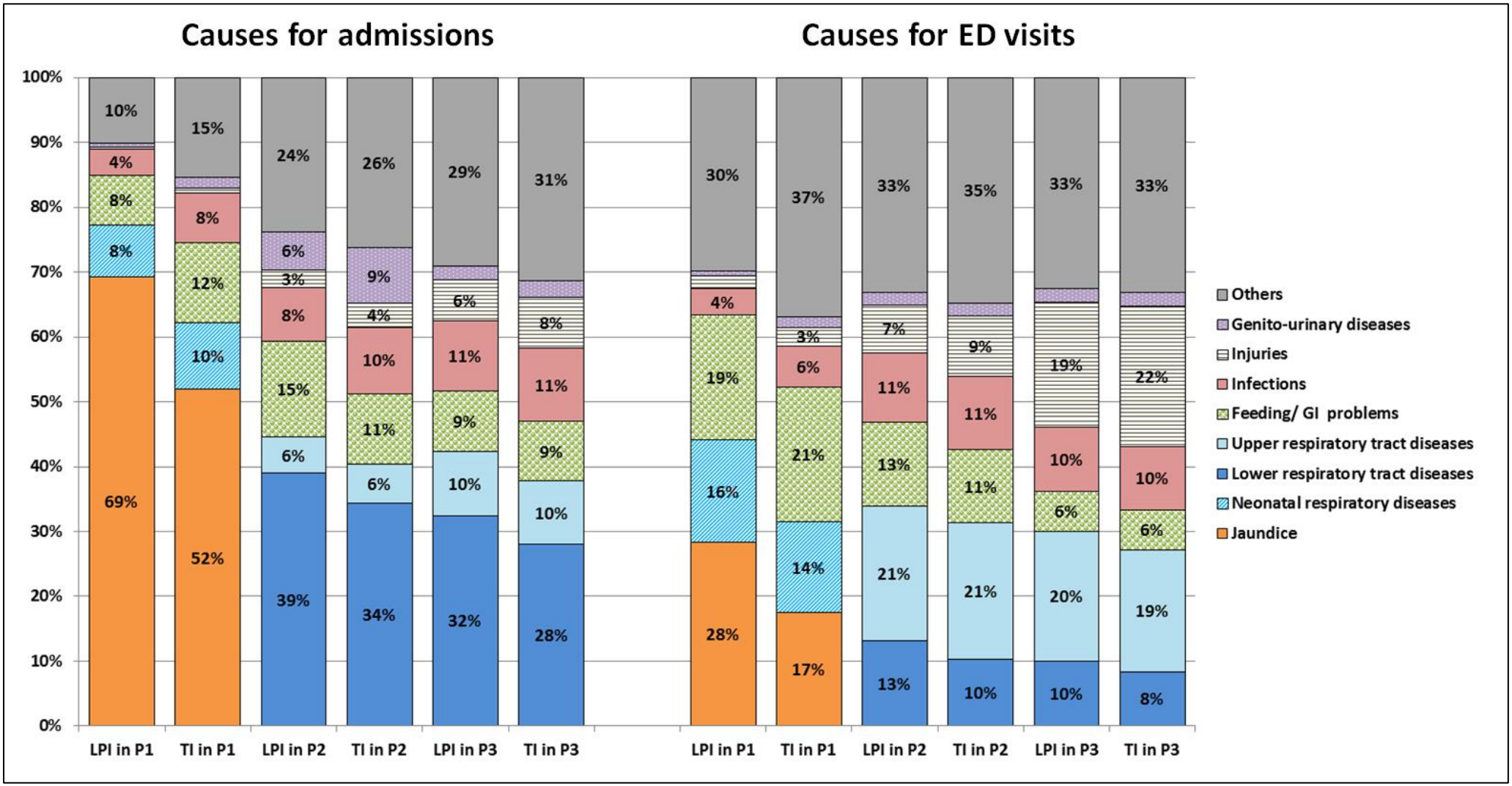
B) Emergency department visits



Abbreviations: 95%CI = 95% confidence intervals; d = days; DCH = discharge home after birth hospitalizations; ED = emergency department; aIRR = adjusted incidence rate ratios; LPI = late preterm infants; TI = term infants; yr = year(s).

The sIRR were estimated using negative binomial regression with generalized estimating equation adjusting for maternal or delivery factors (maternal age, gravida, pre-eclampsia or eclampsia, diabetes, premature rupture of membrane, placental abruption, Caesarean section, oxytocin use, and neighborhood income), infant factors (sex, small for gestational age, neonatal care levels of birth hospitals), and neonatal complications during birth hospitalizations (hypoglycemia, jaundice, cardio-respiratory problems, neurological problems, feeding or gastrointestinal problems, sepsis).

Figure 3: Primary causes for admissions and ED visits in a population-based cohort study of late preterm singletons and twins admissions and ED visits during the first 5 years of life



Abbreviations: ED = emergency department; GI problems = gastrointestinal problems; LPI = late preterm infants; P1 = period 1 after discharge home from birth hospitalizations to 28 days of age; P2 = period 2 from 29 days to 1 year of age; P3 = period 3 from 1 to 5 years of age; TI = term infants.

Supplement

Contents

eTable 1: ICD 10 and CCI codes for covariates in a population-based cohort study of late preterm singletons' and twins' admissions and ED visits during the first 5 years of life

Maternal or delivery covariates	ICD 10 or CCI
Pre-eclampsia / eclampsia	Mothers with O11, O14, O15
Diabetes	Mothers with O24, E10, E11, E13, E14
Premature rupture of membranes	Mothers with O42 Infants with P01.1
Placenta praevia	Mothers with O44 Infants with P02.1
Caesarean section	Mothers with O82, O84.2, CCI of 5.MD.60 Infants with P03.4, Z38.01, Z38.31
Induction of labour with oxytocin	Mothers with CCI of 5.AC.30.AL-I2, 5.AC.30.CA-I2, 5.AC.30.CK-I2, 5.AC.30.HA-I2, 5.AC.30.YA-I2, 5.LD.31.CK-I2, 5.LD.31.HA-I2.
Neonatal covariates	**ICD 10 or CCI**
Twins	Mothers with O30.0, Z37.2, Z37.3 Infants with Z38.3, Z38.4, Z38.5
Hypoglycemia	Infants with P70.0, P70.1, P70.3, P70.4
Neonatal cardio-respiratory problems	Infants with P22-28, P29.3
Neurological disorders of newborn	Infants with P10, P11, P20, P21, P52, P90, P91.0, P91.1, P91.2, P91.6, P91.80
Feeding or gastrointestinal problems of newborns	Infants with E86, E87.0, P74.1, P74.21, P76, P77, P78.0, P78.1, P92, R62.8,
Sepsis	Infants with A40, A41, B37.7, P36
Congenital anomalies or chromosomal abnormalities	Infants with Q00-Q99

Abbreviations: CCI = Canadian Classification of Health Interventions; ICD 10 = the 10th revision of the International Statistical Classification of Diseases and Related Health Problems.

eTable 2: ICD 10 codes for diagnoses for admissions or emergency department visits in a population-based cohort study of late preterm singletons' and twins' admissions and ED visits during the first 5 years of life

Diagnoses	ICD 10 codes
Jaundice	E80.4, E80.5, E80.6, E80.7, P55-59, R17
Feeding or gastrointestinal problems	E86, E87.0, F98.2, P74.1, P74.21, P92, R62.8, R63.3, R63.4, K00-K93, P76-78, P92, R11-15, R18, R19, R68.2
Neonatal respiratory problems (≤ 28 days of age)	J00-J06, J10.0, J10.1, J11.0, J11.1, J12-18, J20-J22, J30-J39, J40-J47, J60-J70, J80-J86, J90-J94, J95-J99, P22-28, R05, R06, U04.9
Lower respiratory tract diseases (> 28 days of age)	J10.0, J11.0, J12-18, J20-J22, J40-J47, J60-J70, J80-J86, J90-J94, J95-J99, U04.9
Upper respiratory tract diseases (> 28 days of age)	J00-J06, J10.1, J11.1, J30-J39
Infections (non-respiratory)	A00-B99, J09, J10.8, J11.8, P35-39
Injuries	S00-T98, V01-X59
Diseases of the genitourinary system	N00-N99, R30-39

Abbreviations: ICD 10 = the 10th revision of the International Statistical Classification of Diseases and Related Health Problems.

eTable 3: Z tests comparing the adjusted incidence rate ratios of singletons with those of twins in a population-based cohort study of late preterm singletons' and twins' admissions and ED visits during the first 5 years of life

Admissions	Singleton	Twins	P value
	aIRR (95%CI)	aIRR (95%CI)	
All 5 yr	1.46 (1.42-1.49)	1.21 (1.11-1.31)	< 0.001
DCH-28d	2.21 (2.13-2.29)	1.40 (1.18-1.66)	< 0.001
29d-1yr	1.50 (1.45-1.56)	1.26 (1.14-1.40)	< 0.001
1-5yr	1.21 (1.16-1.26)	1.15 (1.01-1.31)	0.28
ED visits	**aIRR (95%CI)**	**aIRR (95%CI)**	**P value**
All 5 yr	1.14 (1.12, 1.15)	1.15 (1.11, 1.19)	0.65
DCH-28d	1.28 (1.24, 1.32)	1.13 (1.01, 1.26)	0.03
29d-1yr	1.21 (1.19, 1.22)	1.22 (1.17, 1.29)	0.75
1-5yr	1.12 (1.10, 1.13)	1.14 (1.10, 1.19)	0.40

Abbreviations: 95%CI = 95% confidence intervals; d = days; DCH = discharge home after birth hospitalizations; ED = emergency department; aIRR = adjusted incidence rate ratios; yr = year(s).

The sIRR of late preterm versus term infants were estimated using negative binomial regression with generalized estimating equation adjusting for maternal or delivery factors (maternal age, gravida, pre-eclampsia or eclampsia, diabetes, premature rupture of membrane, placental abruption, Caesarean section, oxytocin use, and neighborhood income), infant factors (sex, small for gestational age, neonatal care levels of birth hospitals), and neonatal complications during birth hospitalizations (hypoglycemia, jaundice, cardio-respiratory problems, neurological problems, feeding or gastrointestinal problems, sepsis).

eTable 4: Z tests comparing the adjusted incidence rate ratios for admissions with those for emergency department visits in a population-based cohort study of late preterm singletons' and twins' admissions and ED visits during the first 5 years of life

	Admissions	ED visits	
Singletons	**aIRR (95%CI)**	**aIRR (95%CI)**	**P value**
All 5 yr	1.46 (1.42-1.49)	1.14 (1.12, 1.15)	< 0.001
DCH-28d	2.21 (2.13-2.29)	1.28 (1.24, 1.32)	< 0.001
29d-1yr	1.50 (1.45-1.56)	1.21 (1.19, 1.22)	< 0.001
1-5yr	1.21 (1.16-1.26)	1.12 (1.10, 1.13)	< 0.001
Twins	**aIRR (95%CI)**	**aIRR (95%CI)**	**P value**
All 5 yr	1.21 (1.11-1.31)	1.15 (1.11, 1.19)	0.27
DCH-28d	1.40 (1.18-1.66)	1.13 (1.01, 1.26)	0.04
29d-1yr	1.26 (1.14-1.40)	1.22 (1.17, 1.29)	0.58
1-5yr	1.15 (1.01-1.31)	1.14 (1.10, 1.19)	0.85

Abbreviations: 95%CI = 95% confidence intervals; d = days; DCH = discharge home after birth hospitalizations; ED = emergency department; aIRR = adjusted incidence rate ratios.
The sIRR of late preterm versus term infants were estimated using negative binomial regression with generalized estimating equation adjusting for maternal or delivery factors (maternal age, gravida, pre-eclampsia or eclampsia, diabetes, premature rupture of membrane, placental abruption, Caesarean section, oxytocin use, and neighborhood income), infant factors (sex, small for gestational age, neonatal care levels of birth hospitals), and neonatal complications during birth hospitalizations (hypoglycemia, jaundice, cardio-respiratory problems, neurological problems, feeding or gastrointestinal problems, sepsis).

CAPTER 4

STUDY C

HEALTHCARE COST AND RESOURCE USE OF EARLY DISCHARGE OF HEALTHY LATE PRETERM AND TERM SINGLETONS

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This manuscript is ready for the submission to JAMA Pediatrics for a peer-review at the time of the submission of this thesis.

TITLE

Healthcare Cost and Resource Use of Early Discharge of Healthy Late Preterm and Term Singleton

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Short title:
Early discharge of Late Preterm and Term Singletons

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Abbreviations: aIRR: adjusted incidence rate ratio; aMCD: adjusted mean cost difference; DAD: Discharge Abstract Database; ED: emergency department; ICES: Institute for Clinical Evaluative Sciences; NICU: neonatal intensive care units; OHIP; Ontario Health Insurance Plan;

Table of Contents Summary: (25/25 words)
Cost and resource use for early, late and very-late discharge after birth (<48, 48-71, 72-95 hours) were compared in healthy late preterm and term singletons.

Contributor's Statement:

Dr Isayama conceptualized and designed the study, developed the study protocol, obtained the approval for data access, conducted the analyses, interpreted the study results, wrote the first draft manuscript, and revised the manuscript. Dr. Isayama had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Drs O'Reilly and Beyene provided advice for designing the study, developing the study protocol, and conducting the analyses, interpreted the study results, and critically reviewed and revised the manuscript.

Drs Shah, and Lee provided advice for developing the study protocol, and critically reviewed and revised the manuscript.

Dr McDonald supervised all aspects of this study, conceptualized and designed the study, developed the protocol, provided advice for conducting the analyses, interpreted the study results, and critically reviewed and revised the manuscript.

All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work**.**

Abstract

Objectives: To assess the healthcare cost and resource use of various discharge timings after birth in late preterm and term infants.

Methods: In healthy vaginally-born singletons at 35-41 weeks gestation in Ontario from 2003-2012, the healthcare costs and number of hospitalizations and emergency department visits were compared between early, late and very-late discharge (<48, 48-71, 72-95 hours after birth) using generalized linear models.

Results: Among 773,213 healthy singletons (late preterm infants = 2.2%), the mean total 1-year cost was not significantly different for late preterm infants between early discharge and late discharge after adjustment (adjusted mean cost difference [aMCD] $40 [95% confidence interval: -$167, $247] per infants; aMCD $242 [-$35, $519] per mother-infant-dyad). However, for term infants, the adjusted cost was higher with early discharge than late discharge (aMCD $ 61 [$18, $104] per infant; aMCD $290 [$235, $344] per mother-infant-dyad). The re-admission rates were higher within 28 days of birth after early rather than late discharge in both late preterm (adjusted incident ratios [aIRR] 1.17 [1.03, 1.32]) and term infants (aIRR 1.16 [1.06, 1.27]), although it was not significantly different for the entire first year. The proportion of early discharge increased significantly over 10 years in term infants (from 69% to 82%, P < 0.001), but not in late preterm infants (from 32% to 35%, P=0.75).

Conclusions: Early discharge was not associated with a cost saving in late preterm infants, and instead was associated with a cost increase in term infants after adjustment over the first year after birth.

BACKGROUND:

The postnatal hospital stay of newborns and mothers has been decreasing in various high-income countries.[1-5] Early discharge was reported to reduce healthcare costs and increased maternal satisfaction.[6] However, there are safety concerns that some medical conditions may be undetected soon after birth and early discharge may increase infants' post-discharge morbidity and mortality.[7-11] In response, since 1996 in the USA, state and federal legislation has mandated that insurance plans cover costs for at least 48 hours after vaginal birth and 72 hours after Caesarean section.[12] This legislation dramatically reduced early postnatal discharge in the USA.[12, 13] In Canada, there is no legislation and, although there are guidelines addressing discharge, they advocate timely follow-up for infants discharged early after birth but do not address a mandatory minimal length of stay.[14-16] The rates of the early postnatal discharge have increased from 2003-5 (38% <1 day, 80% < 2 day) to 2008-10 (47% < 1 day, 84% < 2 day) in vaginally-born term infants in Canada.[17]

Most previous studies of early discharge focused on term infants and data for late preterm infants are scarce. Because late preterm infants have higher morbidity than term infants, the effect of early discharge on post-discharge morbidity and health resource use may be higher for late preterm infants than term infants.[18, 19] Therefore, it is concerning that high proportions of late preterm infants were discharged early after birth (< 2 nights stay), even in settings with legislation such as California (approximately 40%).[20] Although potential cost

saving may be a motivator for early postnatal discharge, data are limited on the healthcare costs following early discharge, especially in late preterm infants. Given the potential increased morbidity after early discharge, there is a need to investigate healthcare costs and resource utilization associated with early discharge of late preterm infants.

Hence, this study evaluated the healthcare costs and hospital re-admission and emergency department visits for the first year after birth in healthy late preterm and term singletons who were discharged early (< 48 hours), late (48-71 hours) or very-late (72-95 hours) in Ontario with a publicly-funded universal health insurance system. The proportion of early discharge and its trend over time were also assessed.

METHODS

Population:

Late preterm and term singleton infants (35-36 and 37-41 weeks gestational age, respectively) born vaginally from 2003 to 2012 in Ontario, Canada, were included in this retrospective population-based cohort study. Ontario has a population of over 13 million and approximately 140,000 live births per year.[21] Late preterm infants born at 34 weeks gestation were excluded because their early discharge is rare due to higher morbidity.[16] Infants were excluded if they were born by caesarean section because they generally stay longer for mothers' postpartum recovery, if they died before initial discharge, had congenital anomalies or

chromosomal abnormalities, were born at home (< 3% of all births in Ontario), or moved out of Ontario before 1 year of age.[22] For the analyses comparing 3 different discharge timings, the study excluded those who were discharged after 96 hours after birth, admitted to neonatal intensive care units (NICU) or transferred to other hospitals before discharge, or whose mother were admitted to intensive care units because they were unlikely to be eligible for early discharge.

Data sources:

The linked administrative databases at the Institute for Clinical Evaluative Sciences (ICES) in Ontario were used including the databases for hospitalizations (Discharge Abstract Database), emergency department (ED) visits (National Ambulatory Care Reporting System), physician billing (Ontario Health Insurance Plan: OHIP), and vital statistics (Registered Persons Database).[23-25] Mother-infant dyads were identified using the MOMBABY database that deterministically linked the mother-infant data.[26] The data coding quality of the databases was previously reported.[25, 27, 28] Re-abstraction studies comparing the original DAD codes and re-abstracted ones found excellent agreement (>97%) for demographic variables (e.g. gender), length of stay, and gestational age, and moderate agreement for the most responsible diagnosis contributing the most to length of hospital stay (76% of the original codes were re-abstracted as diagnoses), although the agreement was less for other types of diagnoses (e.g. comorbidity).[27, 28] These ICES databases have been used to study health outcomes, service use and care cost.[26, 29, 30] Gestational ages were based on the best clinical estimation by

attending physicians or nurses' documentation.[31] The duration of initial length of stay was calculated from the time of birth to infants' first discharge home.

Primary and secondary outcomes:

The primary outcome was the total healthcare cost per infant for the first year after birth. The secondary outcomes were the total health care cost per mother-infant dyad for the first year after birth as well as the rates of re-admission and ED visits. These outcomes were also assessed in 3 partial periods: (1) from birth to initial discharge home (only for costs), (2) from initial discharge home to 28 days after birth, and (3) from 29 days to 1 year after birth. The cost for mothers during the initial hospitalization was estimated from mother's admission to discharge. In addition, the proportion of the early discharge among all discharges and its trend over the study period was assessed.

The healthcare costs were calculated for: (1) hospitalization costs, (2) ED visit costs, and (3) physician billing costs (both inpatient and outpatient) in Canadian dollars ($). All the costs were inflated to those in 2012 using the Consumer Price Index for healthcare in Ontario.[32] Physician billing costs for physician visits or claims were estimated from fees paid directly to physicians according to fee-for-service payments.[33] The other costs such as those for medications, nursing or midwifery services, visits to physicians paid by non-fee-for-service payments, and non-medical costs (e.g. travel expenses) were not included. The cost for hospitalizations and ED visits was estimated by a case-mix costing methodology, in which the cost was estimated from a provincial-average

cost per weighted case multiplied by patients' resource intensity weight.[33, 34] The cost per weighted case is a unit cost indicating a cost of a standard or average patient calculated from all direct and indirect health-care cost for inpatient and emergency department care.[33] The resource intensity weight indicates how much resource a patient consumes relative to a standard patient and was calculated for each patient based on the patient's major diagnosis, procedures, interventions, age, comorbidity level, and length of stay.[33] The detail of the case-mix costing methodology has been described in previous reports.[33, 34]

Analysis:

Comparisons between early, late, and very-late discharge: Baseline characteristics were compared using Chi-square tests. The variable definitions can be found in the eTable 1 in the supplement. Variables significant at $p<0.05$ were included in adjusted analyses as covariates. The mean costs were compared between the 3 groups using generalized linear regression models (GLM) adjusting for maternal and infant covariates and years with a distribution and link function selected based on the smaller Akaike Information Criterion (AIC) recommended by Barber and Thompson.[35] Among multiple potential distributions (Gaussian, over-dispersed Poisson, gamma, inverse Gaussian), the inverse Gaussian distribution was selected for all the GLM except for the cost from 29 days to 1 year, for which the gamma distribution was selected. Although the AIC was smaller with identity link function for late preterm infants and with log link function for term infants, the identity link function was used for both late preterm

and term infants to make the comparison and interpretation of the results straightforward. The results were expressed as adjusted mean cost differences (aMCD). For zero cost, $0.5 was added to the cost because the GLM analysis with Gamma distribution does not allow zero-values. The rates of re-admission and ED visits were compared using negative binomial regression analyses adjusting for maternal and infant covariates. To accommodate the clustering effect among infants born at the same institutions, generalized estimating equations were used in all the adjusted analyses. The analyses were conducted using SAS 9.3 with two-sided α-levels = 0.05.

Trend analysis: The proportion of early discharge (< 48 hours of birth) from 2003 to 2012 was evaluated and the trend of the proportion was assessed using a Cochrane-Armitage trend test. For this trend analysis, all infants born vaginally at 35-41 weeks gestation without congenital anomalies or chromosomal abnormalities were included.

Ethics and sample size:

This study was approved by the Research Ethics Board at McMaster University. The sample size of this study was decided based on the availability of the ICES data using ICD 10^{th} codes (from 2002) and all the cost data (from 2003-2012).

RESULTS:

For the comparison between early, late, and very-late discharge (<48, 48-71, 72-95 hours, respectively), 773,213 healthy infants were included (17,042 late

preterm and 756,171 term infants; Figure 1). Most of the baseline characteristics were significantly different among the groups (Table 1). In particular, infants with early discharge were more likely to be born to mothers with lower neighborhood income, multi-gravida, less premature rupture of membrane, and, at greater gestational ages and had less neonatal complications during initial birth hospitalizations.

Healthcare Cost

The unadjusted mean total 1-year cost was lower in infants who discharge earlier in both late preterm and term infants (eTable 2 in the supplement). However, after adjusting for maternal and infant covariates, the mean total 1-year cost was not significantly different between early and late discharge for late preterm infants (aMCD $40 per infant [95% confidence interval, 95%CI: -$167, $247]), and for term infants the cost was rather higher in early discharge (aMCD $61 per infant [95%CI: $18, $104]; Figure 2A). The mean total 1-year adjusted cost per infant were not significantly different between very-late discharge and late discharge for late preterm infants (aMCD $153 per infant [95%CI: -$207, $513]) but for term infants they were higher in very-late discharge than late discharge (aMCD $103 per infant [95%CI: $21, $185]). Regarding the health-care cost in each period from birth to 1 year of age, the cost of the early discharge group was lower in the initial birth hospitalization than the late discharge group after adjustment; however, it was higher from the initial discharge home to 28 days of age in both late preterm and term infants (Figure 2A). The cost for the very-late discharge

group was higher in the initial birth hospitalization and lower from the initial discharge to 28 days of age than the late discharge group. The comparison of the cost per mother-infant dyad including mothers' cost found similar results (Figure 2B). After adjustment, the total 1-year cost with early discharge was not significantly different in late preterm infants (aMCD $242 per mother-infant-dyad [95%CI: -$35, $519]) but it was higher in term infants (aMCD $290 per mother-infant-dyad [95%CI: $235, $344]) compared with late discharge group (Figure 2B). Among three types of health care cost included, the hospitalization cost, particularly the initial hospitalization, was higher than the cost of ED visits or physician visits in all the periods for both late preterm and term infants regardless of the discharge-timings (eTable 3).

Re-admissions and ED visits after discharge

The re-admission rates for the entire first year were not different between early and late discharge groups in both late preterm and term infants (Figure 3A). However, the re-admission rates up to 28 days after birth was significantly higher with early discharge than late discharge in both late preterm (adjusted incident ratios [aIRR] 1.17 [95%CI: 1.03, 1.32]) and term infants (aIRR 1.16 [95%CI: 1.06, 1.27]) after adjusting for covariates. Very-late discharge was associated with significantly lower re-admission rates than late discharge in the first year after birth in both late preterm and term infants, especially from discharge home to 28 days of birth. The ED-visit rate for the first year after birth was not significantly different between early and late discharge groups in late preterm infants, although

it was significantly lower in term infants (aIRR 0.87 [95%CI: 0.84, 0.91]; Figure 3B).

The trend of the proportions of early discharge (<48 hours) over 10 years

A total of 860,693 infants were included in this analysis (Figure 1). The proportion of the early discharge (<48 hours) increased significantly from 2003 to 2012 in term infants from 69% to 82% (P < 0.001), but not in late preterm infants (32% to 35%, P=0.75; Figure 4).

DISCUSSION

In this large population-based cohort study of singleton infants born at 35-41 weeks gestation in Ontario and not requiring NICU admission during birth hospitalizations, early discharge was not associated with the cost reduction for the first year after birth in late preterm infants, and instead was associated with the 1-year cost increase in term infants ($61 per infant; $290 per mother-infant dyad) after adjusting for covariates. Early discharge was associated with higher re-admission rates than late discharge from discharge to 28 days after birth in both late preterm and term infants, although it was not significant for the entire first year after birth. The proportion of early discharges increased over the study years in term infants, although not in late preterm infants.

The increased readmissions or emergency department visits after early newborn discharge has been disputed in the literature; several studies reported increased re-hospitalization for jaundice, dehydration, feeding problems and

sepsis after early discharge,[8-10] while other studies found no such increases.[13, 36, 37] Potential reasons for the inconsistency in the previous studies could include differences in the definition of early discharge (e.g. < 30 vs. < 48 hours), follow-up periods (e.g. 7 days, 14 days, 28 days), study population (e.g. inclusion or exclusion criteria, racial or socioeconomic profiles), and health care provision (e.g. insurance coverage, post-discharge newborn follow-up, home visit programs).[8-10, 13, 36, 37] The characteristics of our study included healthy infants (i.e. singletons born vaginally not requiring initial NICU admission), relatively late threshold of early discharge (< 48 hours) compared with other studies,[2, 8, 11, 37] and the presence of a guideline recommending early post-discharge follow-up.[14, 15] Because these factors in our study would likely reduce the risk of re-admissions or emergency department visits after early discharge, it was an important finding that the early discharge was still associated with the increased re-admission until 28 days of birth.

Previous data were limited on healthcare costs related to early discharge. A Swiss single center randomized control trial reported that the early discharge of term singletons (24-48 hours for vaginal birth, 72-96 hours for caesarean section) combined with home midwifery support reduced the total societal cost (both indirect and direct cost for infants and mothers) within 28 days of birth by 1221 Swiss franc per case.[38] A Spanish single center randomized control trial reported that early discharge (< 24 hours) of healthy vaginally-born term infants combined with close monitoring at home by qualified nurses saved US$293 per case within

6 weeks after birth compared with traditional initial hospital stay at minimum 48 hours.[39] Unlike these two trials, our study did not find the cost saving by early discharge after adjusting for infants' baseline characteristics and rather the early discharge cost more in term infants likely due to increased re-admission within 28 days of birth. This discrepancy between the previous trials and our study may be because home visiting service by nurses or midwives was not mandatory and likely not common in Ontario in contrast to these previous trials.[14]

Strengths of this study include the large population-based cohort that reduced selection bias, increased statistical power, and captured all readmissions, ED visits, and healthcare cost within the province. Second, the restriction of the study population to healthy vaginally-born singletons not requiring initial NICU admission, along with adjustment for various maternal and infant characteristics minimized biases from the differential selection of discharge timings. Third, the generalized linear model analyses directly provided the adjusted mean cost differences between different discharge timings without any data transformation and the interpretation of the result was straightforward,[35] while accounting for the clustering effect within institutions. Limitations of this study included the observational study design. Even with the adjustment, there may be residual unadjusted confounders. In fact, this study found some unexpected reductions in re-admissions and ED visits by early discharge, especially after 29 days of birth in term infants. This may indicate the presence of unadjusted residual biases that made the early discharge group healthier than others. Given this likely direction of

potential confounding, the true re-admission rates and cost with early discharge may be higher than the current results. Data were not available for some medical or non-medical cost (e.g. medication cost, travel expenses). However, the impact of these other costs is likely small compared to the cost related to hospital service.[38]

Because we did not find a cost saving with early discharge, this should not be the motivation for early discharge. Rather, our finding of the increased adjusted cost by approximately $60 per term infants (or $290 per mother-term infant dyad) for early discharge of 60 thousands term infants per year can be translated to the increase of $3.6 million (or $17.4 million including mothers' cost) per year in the provincial health budget due to early discharge. Therefore, a blanket healthcare strategy or policy to consider length of hospital stay less than 48 hours as good institutional performance for healthy infants after birth needs proper consideration and rethinking. Our study does not indicate that all infants should be discharged more than 48 hours of birth; rather, we suggest an individualized approach may be more appropriate. For identifying such an approach, further evaluation of risk or protective factors associated with re-admissions or ED visits is needed.

CONCLUSION

Early discharge after birth (< 48 hours) was not associated with the reduction of healthcare cost in healthy late preterm infants, and instead was associated with the

cost increase in healthy term infants after adjustment over the first year after birth. Early discharge was also associated with an increased re-admission within 28 days of birth.

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Table 1: Characteristics of infants discharged at < 48, 48-71, 72-95 hours: A population-based cohort study on early discharge of healthy late preterm and term singletons

Singletons born at 35-41 wkGA in 2003-12 by VD			Late preterm infants at 35-36 wk GA (N = 17042)							Term infants at 37-41 wk GA (N=756171)						
			Early DC at < 48 hr (N=9193)		Late DC at 48-71 hr (N=5782)		Very-late DC at 72-95 hr (N=2067)		Chi^2 P values	Early DC at < 48 hr (N=597641)		Late DC at 48-71 hr (N=136053)		Very-late DC at 72-95 hr (N=22477)		Chi^2 P values
Maternal or delivery factors		4: ≥ 37 yr	979	11%	644	11%	211	10%		58435	10%	12755	9%	2367	11%	
	Gravida ≥ 1		6479	70%	3456	60%	1075	52%	<.0001	430663	72%	74160	55%	10810	48%	<.0001
	Preeclampsia/		106	1%	137	2%	80	4%	<.0001	1880	0%	1031	1%	374	2%	<.0001
	Maternal Diabetes		599	7%	403	7%	140	7%	0.5515	22107	4%	4964	4%	999	4%	<.0001
	PROM		3096	34%	2064	36%	858	42%	<.0001	50333	8%	13415	10%	2663	12%	<.0001
	Abruptio placenta		165	2%	134	2%	40	2%	0.0817	2295	0%	653	0%	147	1%	<.0001
	Oxytocin use		2896	32%	1832	32%	755	37%	<.0001	180122	30%	41810	31%	8148	36%	<.0001
	Maternal income	1: low	2206	24%	1286	22%	427	21%		133452	22%	29953	22%	4933	22%	
		2: middle	5586	61%	3562	62%	1272	62%	0.0011	366416	61%	82451	61%	13553	60%	<.0001
		3: high	1401	15%	934	16%	368	18%		97773	16%	23649	17%	3991	18%	
Infant factors	GA	35 wk	1110	12%	1156	20%	531	26%	<.0001	-	-	-	-	-	-	-
		36 wk	8083	88%	4626	80%	1536	74%		-	-	-	-	-	-	-
		37 wk	-	-	-	-	-	-	-	33332	6%	9605	7%	2352	10%	
		38 wk	-	-	-	-	-	-	-	98226	16%	22406	16%	4163	19%	
		39 wk	-	-	-	-	-	-	-	178809	30%	38917	29%	6156	27%	<.0001
		40 wk	-	-	-	-	-	-	-	204013	34%	45839	34%	6739	30%	
		41 wk	-	-	-	-	-	-	-	83261	14%	19286	14%	3067	14%	
	Male sex		4875	53%	3131	54%	1097	53%	0.3858	295130	49%	68625	50%	11496	51%	<.0001
	SGA		134	1%	140	2%	75	4%	<.0001	42599	7%	12185	9%	2383	11%	<.0001
	Neonatal care level of	level 1	1491	16%	753	13%	305	15%		87127	15%	24016	18%	4128	18%	
		level 2	6470	70%	3900	67%	1323	64%	<.0001	436483	73%	84899	62%	13060	58%	<.0001
		level 3	1232	13%	1129	20%	439	21%		74031	12%	27138	20%	5289	24%	
	Hypoglycemia		375	4%	342	6%	163	8%	<.0001	6524	1%	2443	2%	704	3%	<.0001
	Jaundice		162	2%	605	10%	902	44%	<.0001	5689	1%	9311	7%	7755	35%	<.0001
	Feeding/GI problems		76	1%	141	2%	115	6%	<.0001	1908	0%	2000	1%	1171	5%	<.0001
	Cardio-respiratory		241	3%	255	4%	168	8%	<.0001	10187	2%	4500	3%	1419	6%	<.0001
	Neurological problems		17	0%	13	0%	4	0%	0.8658	1140	0%	514	0%	131	1%	<.0001

Abbreviations: DC = discharge; GI problems= gastrointestinal problems; PROM = premature rupture of membrane; SGA = small for gestational age (birth weight < 10 percentile); wk = weeks.

The definitions for these covariates can be found in the eTable 1 in the supplement.

Figure 1: Flow diagram of study participants: A population-based cohort study on early discharge of healthy late preterm and term singletons

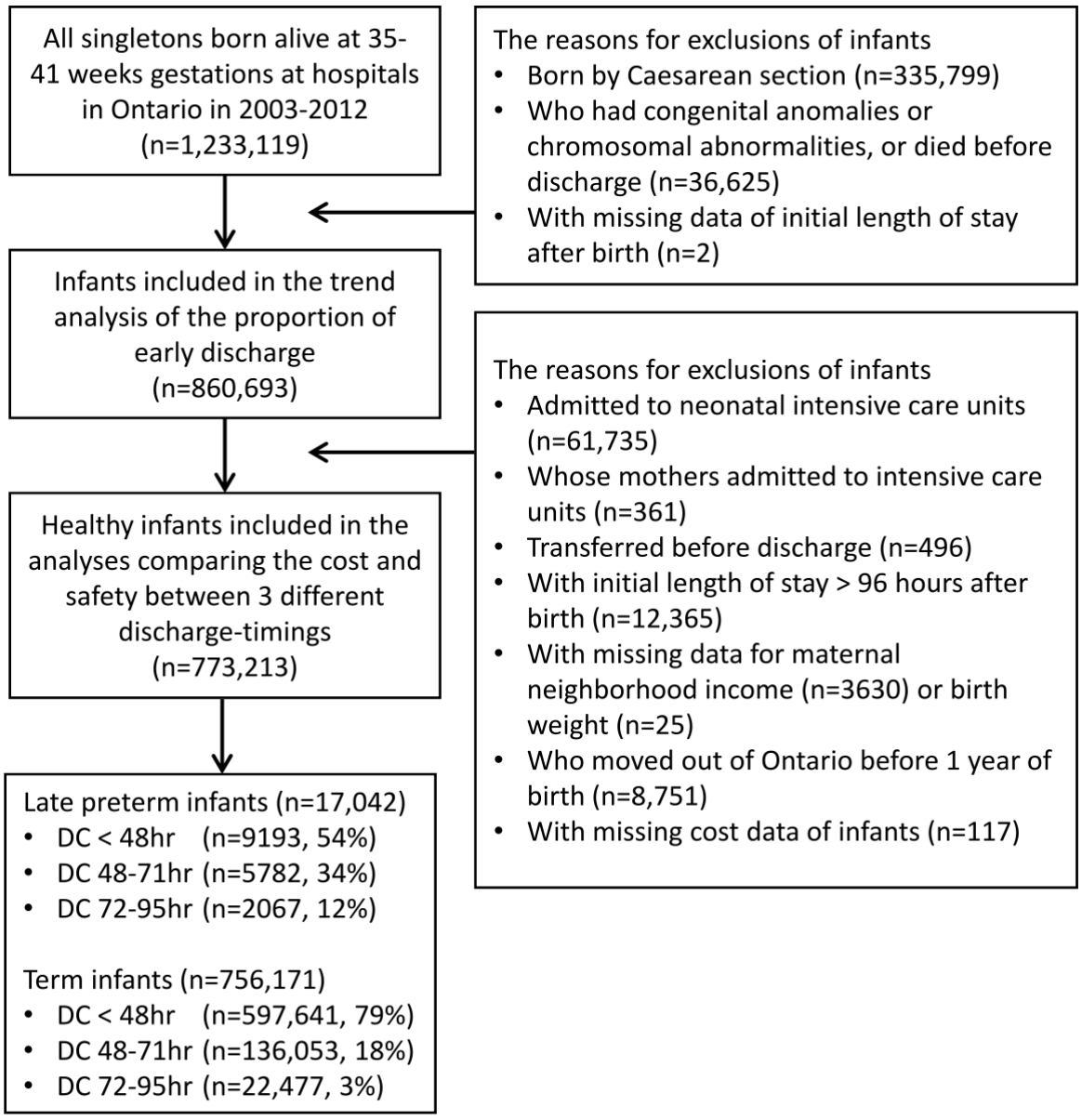
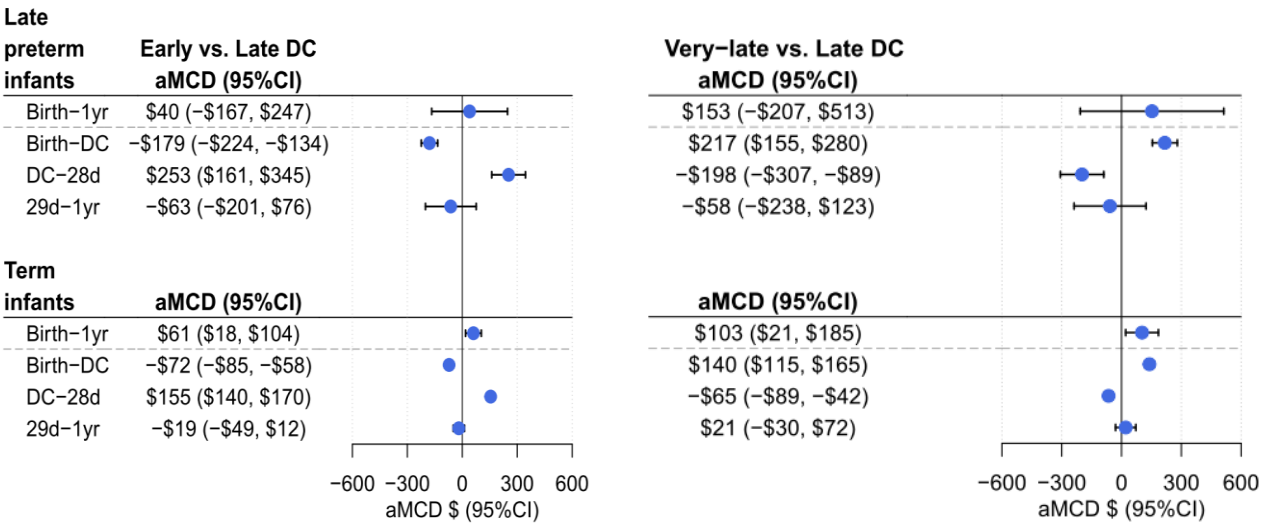
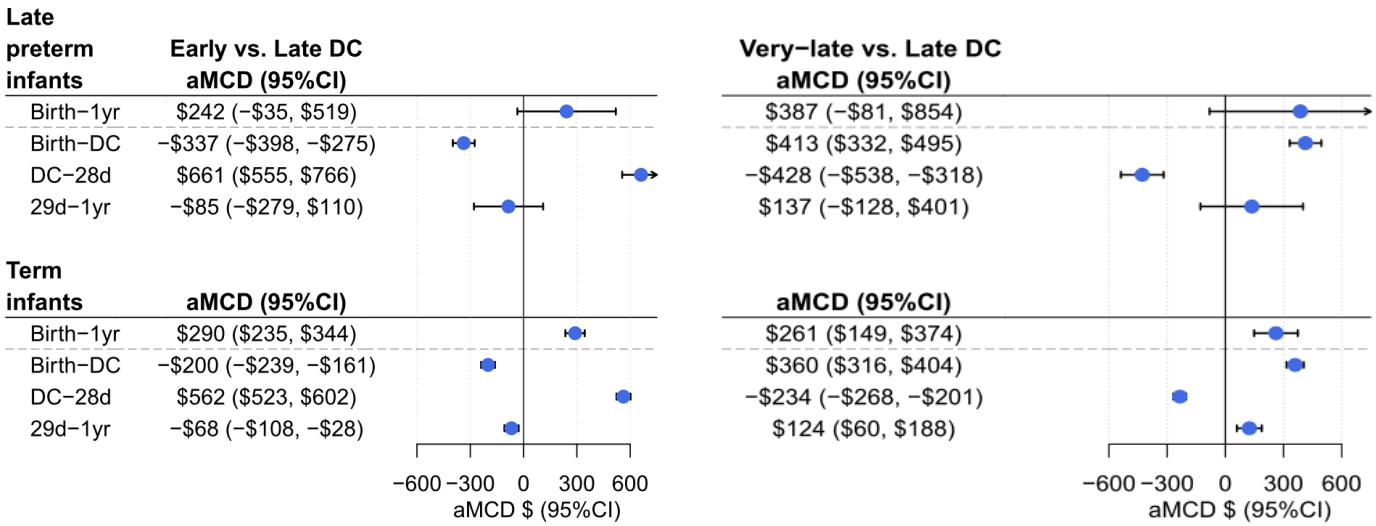


Figure 2: Health care cost for infants with early, late, versus very late discharge (< 48, 48-71, 72-95 hours): A population-based cohort study on early discharge of healthy late preterm and term singletons (35-41 weeks gestational age)

A) Health care cost per infant (not including mother's cost)



B) Health care cost per mother-infant dyad (including mother's cost)



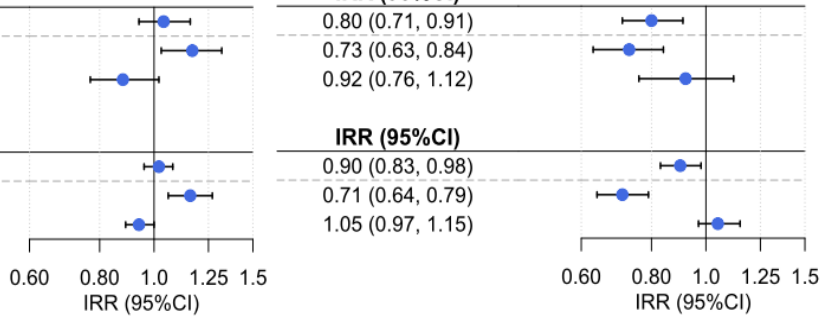
Abbreviations: aMCD = adjusted mean cost differences (Canadian dollars); DC = discharge; 28d (or 29d) = 28 days (or 29 days) of birth; 1yr = 1 year of birth; 95%CI=95% confidence intervals.

The Figure 2A and 2B shows the comparisons of the healthcare costs between 3 different discharge timings per infants (not including mothers' cost) and per mother-infants-dyad (including mothers' costs), respectively. All the costs were inflated to Canadian dollars in 2012. The late discharge group was the reference (control) group for the comparisons and the third columns shows its mean cost (reference cost) in each period from birth to 1 year after birth. The second and fourth columns shows the mean adjusted costs for early and very-late discharge that were calculated by adding the point estimates of the aMCD for "Early vs. Late DC" and "Very-late vs. Late DC" to the reference cost, respectively. The aMCD were estimated by generalized linear models adjusted for maternal characteristics (maternal age [≤18, 19-27, 28-36, ≥37 years of age], multi-gravida, preeclampsia or eclampsia, premature rupture of membranes, oxytocin use, neighborhood income) and infants' characteristics (small for gestational age [< 10 percentile], neonatal care levels of birth hospitals, and infants' complications during birth hospitalizations including hypoglycemia, jaundice, feeding or gastrointestinal problems, cardio-respiratory problems, neurological problems or asphyxia, sepsis) and years for late preterm infants. For term infants, the adjustment was done for the same co-variates as late preterm infants along with maternal diabetes, placental abruption, sex, infants' neurological problems during the birth hospitalizations for term infants.

Figure 3: Re-admission and ED-visit rates for the first year of birth with early (<48hr), late (48-71hr), and very late (72-95hr) discharge: A population-based cohort study on early discharge of healthy late preterm and term singletons (35-41 weeks gestational age)

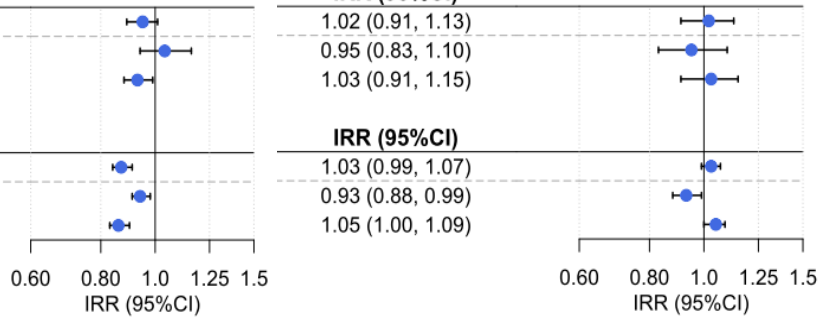
A) Re-admission rates

Late preterm infants	Early DC IR	(Ref.) Late DC IR	Very−late IR	Early vs. Late DC IRR (95%CI)	Very−late vs. Late DC IRR (95%CI)
DC−1yr	227	230	221	1.04 (0.94, 1.16)	0.80 (0.71, 0.91)
DC−28d	142	138	136	1.17 (1.03, 1.32)	0.73 (0.63, 0.84)
29d−1yr	84	92	85	0.88 (0.77, 1.02)	0.92 (0.76, 1.12)
Term infants	**IR**	**IR**	**IR**	**IRR (95%CI)**	**IRR (95%CI)**
DC−1yr	95	97	106	1.02 (0.96, 1.08)	0.90 (0.83, 0.98)
DC−28d	37	37	41	1.16 (1.06, 1.27)	0.71 (0.64, 0.79)
29d−1yr	58	60	65	0.94 (0.89, 1.00)	1.05 (0.97, 1.15)



B) ED visit rates

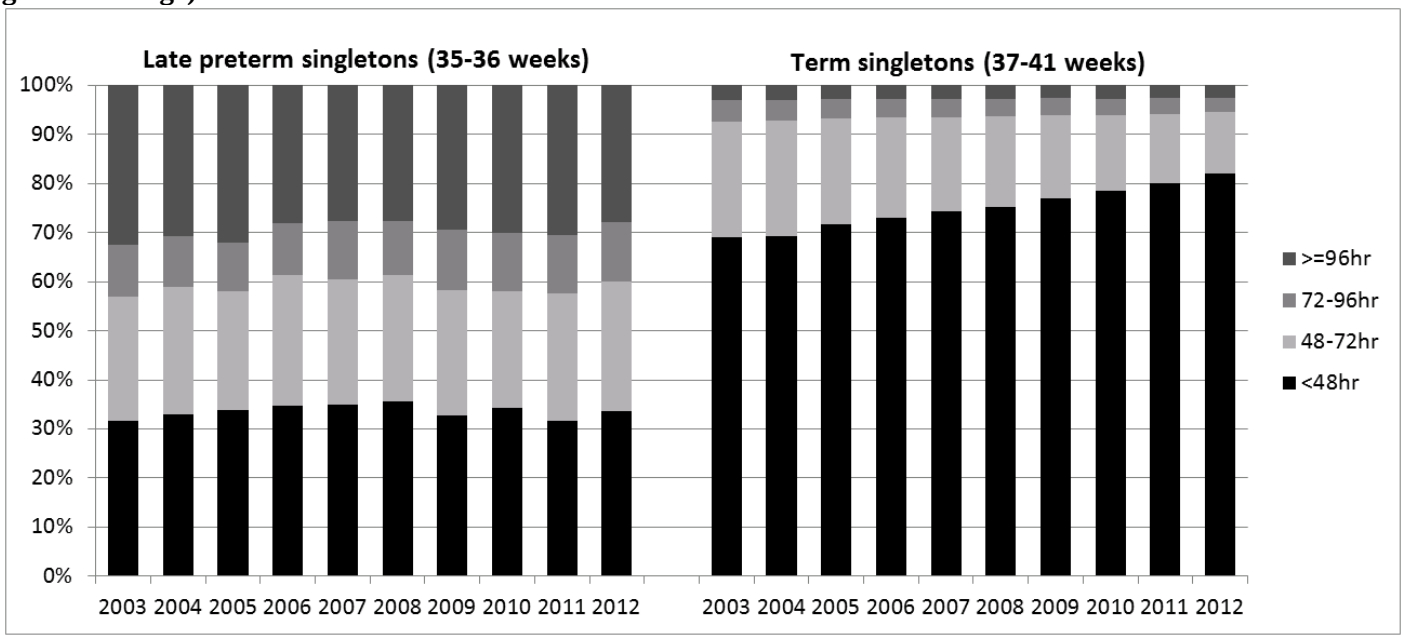
Late preterm infants	Early DC IR	(Ref.) Late DC IR	Very−late IR	Early vs. Late DC IRR (95%CI)	Very−late vs. Late DC IRR (95%CI)
DC−1yr	947	994	1038	0.95 (0.89, 1.01)	1.02 (0.91, 1.13)
DC−28d	164	164	166	1.04 (0.94, 1.16)	0.95 (0.83, 1.10)
29d−1yr	782	830	872	0.93 (0.88, 0.99)	1.03 (0.91, 1.15)
Term infants	**IR**	**IR**	**IR**	**IRR (95%CI)**	**IRR (95%CI)**
DC−1yr	731	874	925	0.87 (0.84, 0.91)	1.03 (0.99, 1.07)
DC−28d	103	118	121	0.94 (0.91, 0.98)	0.93 (0.88, 0.99)
29d−1yr	628	755	804	0.86 (0.83, 0.9)	1.05 (1.00, 1.09)



Abbreviations: DC = discharge; IR = incidence rates per 1000 infants in each period; IRR = adjusted incidence rate ratios; 28d (or 29d) = 28 days (or 29 days) of birth; 1yr = 1 year of birth; 95%CI=95% confidence intervals

The IR (incidence rates) are the number of re-admissions or ED visits per 1000 infants in each period. The IRR (incidence rate ratios) were estimated by negative binomial regression analyses with generalized estimating equations adjusting for maternal characteristics (maternal age [≤18, 19-27, 28-36, ≥37 years of age], multi-gravida, preeclampsia or eclampsia, premature rupture of membranes, oxytocin use, neighborhood income) and infants' characteristics (small for gestational age [< 10 percentile], neonatal care levels of birth hospitals, and infants' complications during birth hospitalizations including hypoglycemia, jaundice, feeding or gastrointestinal problems, cardio-respiratory problems, neurological problems or asphyxia, sepsis) and years for late preterm infants. For term infants, the adjustment was done for the same co-variates as late preterm infants along with maternal diabetes, placental abruption, sex, infants'' neurological problems during the birth hospitalizations for term infants.

Figure 4: The proportion of early discharge (< 48 hours) of singletons born vaginally from 2003 to 2012 in Ontario: A population-based cohort study on early discharge of healthy late preterm and term singletons (35-41 weeks gestational age)



The denominator of the proportion was all the infants born vaginally in hospitals in Ontario without congenital anomaly or chromosomal abnormality. Unlike other analyses in this study, this trend analysis included infants who discharged at ≥ 96 hours or those who admitted to neonatal intensive care units (See Figure 1 for the detail of the inclusion criteria).

Supplement

Contents

eTable 1: Definitions of variables used for inclusion or exclusion criteria or for adjusting in analyses: Healthcare Resource Use and Cost of Early Discharge of Healthy Late Preterm and Term Singleton

Maternal or delivery variables	ICD 10 or CCI or other explanations
Pre-eclampsia / eclampsia	Mothers with O11, O14, O15
Diabetes	Mothers with O24, E10, E11, E13, E14
Premature rupture of membranes	Mothers with O42 Infants with P01.1
Caesarean section (used for exclusion)	Mothers with O82, O84.2, CCI of 5.MD.60 Infants with P03.4, Z38.01, Z38.31
Induction of labour with oxytocin	Mothers with CCI of 5.AC.30.AL-I2, 5.AC.30.CA-I2, 5.AC.30.CK-I2, 5.AC.30.HA-I2, 5.AC.30.YA-I2, 5.LD.31.CK-I2, 5.LD.31.HA-I2.
Maternal neighborhood income levels	The maternal neighborhood income levels (low = the lowest quintile, medium = the second to fourth quintiles, high = the highest quintile) were based on maternal postal code using Statistics Canada census data.[1]
Neonatal variables	**ICD 10 or CCI or other explanations**
Birth hospitals' level of newborn-care	The birth hospitals' level of newborn-care was defined according to the provincial designation as: level 1 (basic care), level 2 (moderately advanced care), or level 3 (highly advanced care).[2]
Hypoglycemia	Infants with P70.0, P70.1, P70.3, P70.4
Neonatal cardio-respiratory problems	Infants with P22-28, P29.3
Neurological disorders of newborn	Infants with P10, P11, P20, P21, P52, P90, P91.0, P91.1, P91.2, P91.6, P91.80
Feeding or gastrointestinal problems of newborns	Infants with E86, E87.0, P74.1, P74.21, P76, P77, P78.0, P78.1, P92, R62.8,
Sepsis	Infants with A40, A41, B37.7, P36
Congenital anomalies or chromosomal abnormalities	Infants with Q00-Q99

Abbreviations: CCI = Canadian Classification of Health Interventions; ICD 10 = the 10th revision of the International Statistical Classification of Diseases and Related Health Problems.

eTable 2: Unadjusted mean total healthcare cost per infant or per mother-infant-dyad in each period from birth to 1 year of age in infants discharged early, late, and very late: Healthcare Resource Use and Cost of Early Discharge of Healthy Late Preterm and Term Singleton

		Late preterm infants Unadjusted mean cost ($)			Term infants Unadjusted mean cost ($)		
		Early DC (<48 hr) N=9193	Late DC (48-71 hr) N=5782	Very-late DC (72-95 hr) N=2067	Early DC (<48 hr) N=597641	Late DC (48-71 hr) N=136053	Very-late DC (72-95 hr) N=22477
Per infant	Birth-1yr	4,676	4,967	5,961	2,673	2,796	3,386
	Birth-DC	2,013	2,457	3,425	1,083	1,286	1,784
	DC-28d	1,538	1,358	1,417	749	630	667
	29d-1yr	1,125	1,152	1,120	842	879	935
Per mother-infant-dyad	Birth-1yr	11,275	11,353	12,443	8,401	8,384	9,028
	Birth-DC	6,314	6,918	8,052	4,827	5,238	5,918
	DC-28d	3,093	2,481	2,266	2,155	1,625	1,438
	29d-1yr	1,868	1,954	2,125	1,419	1,521	1,672

Abbreviation: DC = discharge home after birth; ED visits = emergency department visits; hr, hours; N, number of infants; 28d (or 29d) = 28 days (or 29 days) after birth; 1yr = 1 year after birth.

The costs in the table are unadjusted mean cost per infant or per mother-infant-dyad in Canadian dollars. The study period was from 2003 to 2012 and all the cost were inflated to the cost in 2012 using Consumer Price Index for health care in Ontario.[3]

eTable 3: Unadjusted mean cost for hospitalization, emergency department visits, and physician billing per infant or per mother-infant-dyad in each period from birth to 1 year of age in infants discharged early, late, and very late: Healthcare Resource Use and Cost of Early Discharge of Healthy Late Preterm and Term Singleton

			Late preterm infants Unadjusted mean cost ($)			Term infants Unadjusted mean cost ($)		
			Early DC (<48 hr) N=9193	Late DC (48-71 hr) N=5782	Very-late DC (72-95 hr) N=2067	Early DC (<48 hr) N=597641	Late DC (48-71 hr) N=136053	Very-late DC (72-95 hr) N=22477
Per infant	Hospitalization cost	Birth-DC	1,883	2,291	3,211	996	1,170	1,621
		DC-28d	1,281	1,139	1,200	590	476	503
		29d-1yr	493	509	485	306	313	351
	ED visits cost	DC-28d	44	42	41	24	27	27
		29d-1yr	156	164	169	120	141	148
	Physician billing cost	Birth-DC	129	166	214	87	116	163
		DC-28d	212	177	176	135	127	137
		29d-1yr	476	480	466	416	425	436
Per mother-infant-dyad	Hospitalization cost	Birth-DC	5,137	5,662	6,710	3,710	4,016	4,596
		DC-28d	2,736	2,187	1,966	1,888	1,392	1,185
		29d-1yr	669	737	860	416	443	513
	ED visits cost	DC-28d	61	61	64	40	48	51
		29d-1yr	256	261	289	193	230	251
	Physician billing cost	Birth-DC	1,177	1,255	1,343	1,117	1,222	1,321
		DC-28d	295	234	236	227	185	202
		29d-1yr	943	957	976	810	848	908

Abbreviation: DC = discharge home after birth; ED visits = emergency department visits; hr, hours; N, number of infants; 28d (or 29d) = 28 days (or 29 days) after birth; 1yr = 1 year after birth.

The costs in the table are unadjusted mean cost per infant or per mother-infant-dyad in Canadian dollars. The study period was from 2003 to 2012 and all the cost were inflated to the cost in 2012 using Consumer Price Index for health care in Ontario.[3]

Reference for supplement

1. Wilkins R. Use of postal codes and addresses in the analysis of health data. *Health Rep*. 1993;5(2):157-177.
2. Provincial Council for Maternal and Child Health. Ontario Maternal and Newborn Level of Care Designations. 2017. Available from: http://www.pcmch.on.ca/wp-content/uploads/2015/09/LOC_Designations_-2014SEP08.pdf *(Accessed Jan 18, 2017)*.
3. Statistics Canada. Table 326-0021 - Consumer Price Index, annual (2002=100 unless otherwise noted), CANSIM (database). Available from: http://www5.statcan.gc.ca/cansim/a26?lang=eng&retrLang=eng&id=3260021&&pattern=&stByVal=1&p1=1&p2=-1&tabMode=dataTable&csid= (Accessed Apr 26, 2017).

CHAPTER 5:
CONCLUSION

This thesis investigated various aspects of health service utilization of late preterm and term infants through 3 studies with different research methodologies (a systematic review, a population-based cohort study, and a cost analysis study, respectively) with the aim to fill important knowledge gaps in each area.

Summary of conclusions for study A

To understand current evidence base, study A systematically summarized the health service utilization of late preterm infants compared with those of term infants. This was the first systematic review to specifically investigated health service utilization of late preterm infants, and found that, after discharge from birth hospitalization, late preterm infants had increased hospitalization compared with term infants that persisted from the neonatal period through adolescence, although the degree of the differences became smaller as the infants became older. In addition, the increased health service use was found for a wide variety of specific causes such as jaundice, infection, respiratory problems, asthma, neurological or mental health problems in different developmental stages (e.g. the neonatal period, infancy, early childhood, school age, adolescence, adulthood).

This finding of the long-lasting, increased health service utilization of late preterm infants, which is the largest group of preterm infants, indicated that the prevention or management of late preterm infants may have a substantial impact on health resource use and cost. This information would be of interest to health policy makers and guideline developers. Furthermore, the information of a wide range of cause-specific health service use of late preterm infants in each developmental stage summarized in study A would be useful for health care providers and families of late preterm infants to understand and prepare for the needs of these children in the future.

Methodological limitations of study A

There were several limitations in study A including the observational design of included studies, variations in the effect estimates (e.g. odds ratios, relative risks, incidence rate ratios), and considerable heterogeneity in the results. In particular, the considerable heterogeneity was not explained solely by potential effect modifiers assessed. Although regional differences in health care systems (e.g. insurance systems, discharge policy, types of post-discharge follow-up, home visiting service) may be one of the reasons for the remaining heterogeneity, it is

yet to be investigated by future research. Among these potential factors, the impact of discharge timing from initial birth hospitalization was investigated in study C of this thesis.

Summary of conclusions for study B

As a result of the limited information regarding twins, ED visits, and Canadian long-term data discovered by study A, study B evaluated the re-admissions and ED visits by late preterm and term singletons and twins for the first 5 years after initial birth hospitalizations using a large population-based, administrative database in Ontario. Study B demonstrated that late preterm infants had higher re-admission rates than term infants for the first 5 years after initial discharge and that the increase in rates reduced as infants became older. These results were consistent with previous studies summarized in study A, and re-affirmed these findings in a Canadian population with a publicly-funded, universal health insurance. The assessment of Canadian data was important because study A indicated that the health service use might vary depending on health service systems, regions, or countries. In fact, the differences in the re-admission rates between late preterm and term infants were significantly smaller in Ontario, as

assessed by study B, than another population-based cohort study from Western Australia (Slimings 2014)[48], which was included in study A. The cohort by Slimings 2014[48] was the only study whose results were comparable with those of study B (the incidence rate ratios [95% confidence intervals] in Ontario vs. Western Australia = 2.12 [2.13, 2.29] vs. 2.62 [2.52, 2.72], 1.50 [1.45, 1.56] vs. 2.10 [2.04, 2.15], 1.21 [1.16, 1.26] vs. 1.49 [1.46, 1.52] in the neonatal period, infancy, and early childhood, respectively; Figure 2B in the study A, Figure 2A in the study B). Furthermore, study B revealed that the readmission rates were lower in twins than in singletons and that the differences between late preterm and term infants were smaller in twins than in singletons. The reason for this finding was unclear and is worth investigating in the future. In addition, study B found that the differences in rates between late preterm and term infants were smaller for ED visits than for re-admissions. These study findings would be useful for pre-discharge parental or family education. These results also indicated the need for close post-discharge follow-up for late preterm infants, whether they are singletons or twins.

Methodological limitations of study B

While the use of administrative databases such as the ICES for research has several strengths including efficient or economical access to the data, coverage of almost entire population, and ability to follow-up patients for a long period, there are also unique limitations or issues to consider with it.[29] First, because the data was routinely collected for administrative purposes, not for research purposes, the data collection may have missing data or some variables may have less data accuracy than data collected purely for research purposes. The data coding quality of the ICES databases has been regularly assessed by re-abstraction studies.[33, 49] Based on an ICES report, the demographic variables (e.g. gender, age, birthdate, admission or discharge date) had very high agreement (>98%) between original data and re-abstracted record.[33] The data on the primary outcome (number of admissions) would be anticipated to be very well coded as they are essential information for administrative purposes. The primary causes for admissions and ED visits, evaluated in study B (Figure 3 of study B), are also reported to be reliable, particularly compared with other secondary diagnoses.[33] On the other hand, the co-variates used for the adjustment may have lower reliability because

they were generally secondary diagnoses.[33] Another potential issue is that ICES DAD databases only captured infants born in the hospitals, and hence study B did not included infants born out of hospitals (e.g. home deliveries). However, a majority of deliveries occurred in hospitals in Ontario (97% of deliveries) and the impact of the exclusion of infants born out of hospitals were considered minimal. In addition, because administrative databases generally have a large sample size, the distinction between clinical significance and statistical significance of the results should be considered.[29] For this reason, study B as well as study C presented the results with not only p-values but also 95% confidence intervals to show the range of uncertainty of the effect estimates (e.g. incidence rate ratios) as well as presenting the crude admission or ED visits rates (e.g. unadjusted incidence rates).

Summary of conclusions for study C

Study C assessed the safety and health care costs related to three different discharge timings of late preterm and term singletons: early (< 48 hours), late (48-71 hours), and very-late (72-95 hours) discharge after birth. Although studies A

and B showed the increased health service utilization of late preterm infants than term infants in a long-term period after initial discharge, the information regarding interventions such as early discharge after birth was limited for late preterm infants. Hence, study C investigated how different discharge timings of initial birth hospitalizations affect the re-admissions, ED visits, and the health care cost of healthy late preterm and term vaginally-born singletons. This study found that early discharge increased the number of re-admissions within 28 days after birth compared with late discharge. However, unlike the pre-study expectation that early discharge might be cost-saving, it was not associated with the reduction of health care cost for the first year after birth in late preterm infants, and instead was associated with an increase in the cost in term infants over the first year after birth. This is likely due to the increased number of re-admissions after discharge. This finding would be important for health policy makers and guideline developers as well as care providers to decide the optimal timing of discharge for individual late preterm or term infants. This result indicated that early discharge should not be done for the purposes of saving cost. Rather, the decision on discharge timing should be individualized and the potential risks of increased re-

admissions found in the study should be balanced against the potential benefits (e.g. early family support at home, increasing bonding) as well as other individual conditions (e.g. mothers' confidence, post-discharge support system).

Methodological limitations of Study C

The same limitations or issues related to the use of administrative databases as discussed for study B need to be considered for study C. Because the primary exposure (discharge timing or initial length of stay) in study C was derived from core administrative variables of admission and discharge time, the data reliability was considered high based on the ICES report of re-abstraction studies.[33] On the other hand, the primary outcome (health-care cost for the first year after birth) was estimated using a case-mix costing methodology describe in the method section of the manuscript of study C. Because the method used a cost estimation based on the cost data from some hospitals, not all hospitals, in Ontario, there may be a bias in the cost estimation due to the biased selection of these hospital. Furthermore, because study C estimated the physician billing cost from fee-for-service payments, the payment other than fee-for-service was not included in study C as well as other type of costs including prescription drug costs, nursing or midwifery

services' cost, and non-medical cost. Another limitation in study C was that it focused on vaginally-born singletons and did not provide the information about multiple births (e.g. twins) and infants born by caesarean section. This restriction of the population was necessary because the discharge timing of twins or those born by caesarean section is likely longer than vaginally-born singletons.[50, 51] Because the impact of early discharge on health resource use and cost for twins or infants born by caesarean section may be different, it is yet to be studied. Another limitation was that study C did not assess the use of early post-discharge follow-up nor the use of nursing or midwifery home visiting services after early discharge. Some previous studies reported that early discharge followed by early follow-up or home visit services did not increase re-admissions.[52, 53] Although the guideline from the Canadian Paediatric Society recommends early follow-up within 48 hours after discharge for late preterm infants,[54] the data regarding the early post-discharge follow-up were unavailable for study C. These points are areas for future study.

Overall summary and future direction

This thesis revealed that late preterm infants had increased health service utilization such as re-admissions and ED visits compared with term infants from infancy through adolescence for various causes. The difference between late preterm and term infants was greater in singletons than in twins and for re-admissions than for ED visits. These differences reduced as the children became older. The early discharge after birth increased the re-admissions within 28 days of birth and did not save health care cost in both late preterm and term infants for the first year of birth. These results would be useful for parents or families, healthcare providers, health policy makers and guideline developers to provide optimal health care to late preterm infants.

This thesis also revealed several areas for future research of late preterm infants including the impact of different healthcare system (e.g. insurance systems, types of post-discharge follow-up, home visiting service) on health service utilization, the reasons for the lower rates of hospital service utilization of twins than singletons, impact of early discharge on health service utilization and cost in twins or infants born by caesarean section. Because the impact of

gestational age (e.g. late preterm) and discharge timing on health service utilizations may be different between different regions, or countries, the reassessment of the results of study B and C in future research in other settings would be useful.

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