CESAREAN SECTION DELIVERY IN INDIA:
AN ANALYSIS OF MATERNAL FACTORS AND INFANT OUTCOMES

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ABSTRACT

Cesarean section (CS) delivery is increasing globally, in many countries exceeding the World Health Organization recommended upper limit of 15% of births in all regions. The CS rate is also increasing nationally in India, where the factors and outcomes associated with CS have not previously been explored.

We sought to determine maternal factors and infant outcomes associated with mode of delivery in India from two data sources. First, we assessed the independent association of several maternal factors with mode of delivery in the Longitudinal Indian Family Health (LIFE) study cohort. Second, we assessed whether mode of delivery in the LIFE study was associated with diarrhea and respiratory infection in infants. Lastly, we assessed the maternal, socioeconomic, and healthcare factors, and infant outcomes associated with mode of delivery in the 2005-2006 India National Family Health Survey.

Of the 1,164 singleton births in the LIFE study between 2010 and 2015, 46% were delivered by CS. Prior pregnancy complications, history of prior CS, pre-pregnancy body mass index, and labor and delivery complications contributed to the high CS rate. In regards to infant outcomes, after adjusting for pre-delivery maternal factors, mode of delivery was not associated with infants having diarrhea or respiratory infection at six months in the LIFE study. In the India national data, 12% of the 35,601 most recent singleton births in the 2005 and 2006 survey were delivered by CS. Factors associated with CS nationally were high wealth index, high level of maternal education, maternal receipt of >5 antenatal care visits, and delivery at a private care facility. After adjusting for these factors, mode of delivery was not associated with infant diarrhea and acute respiratory infection, but an association was found with neonatal death.

Our studies yield public health significance in showing that a range of maternal factors are associated with mode of delivery in India, and that mode of delivery is not a determinant of some adverse infant health outcomes. Further research is needed on the effect of CS delivery on infant and maternal outcomes in India and other countries as the CS rates continue to increase.

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PREFACE

Completing this dissertation would not have been possible without the guidance of my advisor, Catherine Haggerty, who encouraged me throughout my doctoral program with patience and kindness. I appreciate my dissertation committee and their invaluable input and time taken to shape my project – Dr. Tang for his expertise in statistics, Dr. Bunker for her wealth of knowledge on India, and Dr. Simhan for his clinical advice. Special thanks also to Marnie Bertolet, Lori Sarracino Smith, Debbie Bass, Ellen Mooney, and the Department of Epidemiology for their support throughout my time at Pitt.

I had the amazing opportunity to travel to India to learn more about my research population and conduct an independent study. I'm so grateful to the India Nationality Room Committee for awarding me with a travel scholarship, and to the SHARE INDIA faculty and staff for their hospitality during my six week stay in Hyderabad.

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I am so thankful for the perpetual support of my parents, Rabecca and Michael, my siblings, and my extended family in Zambia. I dedicate my dissertation to my late grandfather, Alexander Caseby Harawa, a beloved educator who instilled in me at a young age the importance and value of education.

Finally, I am eternally grateful to almighty God for every opportunity that I have been blessed with. His faithfulness and mercy never cease to amaze me; *For of Him, and through Him, and to Him, are all things: to Whom be glory forever. Amen. (Romans 11:36).*

1.0 INTRODUCTION

1.1 BACKGROUND

The World Health Organization (WHO) recommends that the cesarean section (CS) delivery rate should not exceed 15% of births in any region, and should only be used in medically indicated circumstances in order to minimize risks to the infant or the mother.[1,2] However, the rate of CS delivery is increasing worldwide and is not always performed due to medical necessity.[3] As CS delivery is a surgical procedure, there is potential for complications to arise during and after the delivery process.[4] Studies have shown an association between CS and adverse maternal and infant outcomes compared to spontaneous vaginal birth, including higher rates of maternal admittance to the intensive care unit postpartum, and higher incidence of respiratory distress in infants.[5,6] Furthermore, the increase in the CS rate has not coincided with a decrease in perinatal or maternal mortality worldwide.[5]

The **L**ongitudinal **I**ndian **F**amily h**E**alth (LIFE) Study is a prospective cohort study in Telangana State, India, that enrolled 1,227 married, reproductive-aged women pre-pregnancy or in their first trimester of pregnancy, and follows their infants through childhood. Approximately 46% of pregnancies since 2010 have been delivered via CS, [7] compared to an estimated 17% nationally in India, 33% in the USA, and 19% globally.[8] [9] The LIFE study was established to assess the effect of pre-pregnancy maternal behavior, lifestyle, and environment on birth outcomes and child development in a rural to peri-urban area. The overarching goal of this dissertation is to assess the maternal factors associated with mode of delivery, evaluate the infant health outcomes by mode of delivery in the LIFE study, and compare these findings to nationwide survey data obtained from the Indian National Family Health Survey (NFHS).

1.2 RESEARCH AIMS

The goals of this dissertation are the following:

1) To determine the maternal factors associated with mode of delivery in the Longitudinal Indian Family hEalth (LIFE) study cohort

Hypothesis 1: Women in the LIFE study who deliver by cesarean section will have different demographic, reproductive history, anthropometric, antenatal care, prenatal health, and labor and delivery factors than women who deliver vaginally.

2) To assess the impact of mode of delivery on short-term infant health outcomes in the Longitudinal Indian Family hEalth (LIFE) study cohort

Hypothesis 2: Infants in the LIFE study born by cesarean section will have higher reports of diarrheal and respiratory disease at six months compared to those delivered vaginally.

3) To determine the maternal factors and infant health outcomes associated with mode of delivery in India using national survey data

Hypothesis 3a: Women surveyed in the 2005-2006 India National Family Health Survey who delivered by cesarean section will have different demographic, antenatal care, prenatal health, and reproductive history factors than women who delivered vaginally.

Hypothesis 3b: Children of women surveyed in the 2005-2006 India National Family Health Survey born by cesarean section will have higher reports of neonatal deaths, and diarrheal and respiratory disease compared to those delivered vaginally.

2.0 BACKGROUND AND SIGNIFICANCE

2.1 MODE OF DELIVERY

Mode of delivery refers to the passage of a fetus from a pregnant woman either vaginally or by cesarean section (CS). CS is an ancient surgical procedure whereby the fetus is delivered from an incision in the mother's abdomen and uterus. [4,10] CS operation is speculated to have been conducted in ancient India and Egypt to extract infants from mothers who died in childbirth, likely due to obstructed labor, and live birth by CS has been recorded as early as 508 B.C. in Sicily.[10] Maternal mortality associated with CS delivery due to infection or hemorrhage remained high, at rates up to 85%, until the 19th century. [10,11] Improvement in sanitation practices in the 19th century led to a reduction of medical infection overall. Over the last century, maternal mortality in labor and both vaginal and CS delivery has decreased significantly, due in large part to improvements in medical technology and practice.

2.1.1 Current Issues

2.1.1.1 Increasing Rate of Cesarean Sections

While CS as an intervention can be life-saving when medically indicated, there is currently a lack of consensus as to whether the increasing CS rate in both developing and developed countries is warranted.[3] The optimal rate of five to 15% of all births was decided by the WHO in 1985 based on observed CS rates from countries in northern Europe. [1,12] There has been debate on whether this threshold is still valid, especially as CS rates increase. A systematic review of ecologic studies found that the optimal CS rate was nine to 16% of births.[12] There was no decrease in infant or maternal mortality found above this threshold. However, majority of the eight studies in the review, which included national data from low, middle and high income countries, did not control for confounders in the relationship between mode of delivery and maternal mortality, and this may have biased the findings. There remains a major challenge to decrease CS rates in areas where the prevalence is already high.

In the United States the estimated CS rate increased from 20.7% in 1996 to 32.8% in 2012, an increase that has been attributed by some to changes in obstetric practice rather than an increase in medical indications for CS or cesarean delivery on maternal request (CDMR).[13,14] The obstetric changes cited are increases in primary CS not due to medical indication, and a decrease in the practice of vaginal birth after CS (VBAC), resulting in an increase in repeat CSs.[14] Analysis of US national data has shown that the overall CS rate is mostly attributed to increases in primary CS with no indicated risk i.e. full term, singleton, and no medical risk factor reported on the birth certificate. [15]

2.1.1.2 Comparing Cesarean Section Rates

Until 2001 there was no standardized system to compare CS rates. Some countries contribute more data than others in global comparisons, and the validity of findings depend on the quality of national health system data available. Comparisons have been made between private and public health facilities, which are known to serve different populations with varying obstetric characteristics (case mix), adding to the difficulty of obtaining population- level CS rate recommendations. [16]

A ten group classification system, also known as the Robson classification, is an attempt to categorize CS delivery on maternal and fetal indication. The WHO advocates for its implementation in health care institutions. [16] This classification system is based on five obstetric characteristics, creating 10 mutually exclusive groups described in Table 1: parity (nulliparous or multiparous, previous CS), onset of labor (spontaneous, induced, or CS with no labor), gestational age (<37 weeks or >37 weeks), fetal presentation (cephalic, breech, or transverse), and number of fetuses (single or multiple). [16,17] This standardized method is useful for comparing CS rates within and across health facilities by obstetric characteristics before delivery, and researchers are using it as a tool to assess their obstetric populations.[18]

Table 1 The Robson Ten Group Classification System for Cesarean Sections

GROUP	PREGNANCY CHARACTERISTICS
1	Nulliparous, single cephalic pregnancy, ≥37weeks gestation, spontaneous labor
2	Nulliparous, single cephalic pregnancy, ≥37weeks gestation, induced or cesarean before labor
3	Multiparous (excluding previous cesareans), single cephalic pregnancy, ≥37weeks gestation, spontaneous labor
4	Multiparous (excluding previous cesareans), single cephalic pregnancy, ≥37weeks gestation, induced or cesarean before labor
5	Previous cesarean, single cephalic pregnancy , ≥37weeks gestation
6	All nulliparous breeches
7	All multiparous breeches (including previous cesareans)
8	All multiple pregnancies (including previous cesareans)
9	All abnormal lies (including previous cesareans)
10	All single cephalic pregnancies, ≤36weeks gestation (including previous cesareans)

2.1.1.3 Vaginal Birth after a Previous Cesarean

Vaginal birth after cesarean (VBAC) was proposed as a method to prevent repeat CS in the 1980s after observational evidence showed fewer complications in women who delivered vaginally after a previous low-transverse CS compared to those who had an elective repeat CS.[19] This led to the American College of Obstetrics and Gynecology (ACOG) developing VBAC guidelines, which have been cited internationally. [20] These guidelines were updated in 2011 to encourage obstetricians in trial of labor after a previous cesarean (TOLAC) after a noted decrease in VBAC and increase in CS in the United States. [21] Some of the resistance to conducting VBACs stemmed from the risk of uterine rupture with TOLAC following classical or T-shaped CS incisions, which are performed on the upper segment of the uterus. [20,22] However, the risk of uterine rupture following a lower-segment transverse or vertical CS has been found to be less than 1%.[22] Obstetric fistula, previous ruptured uterus, short inter-pregnancy interval, and cephalo-pelvic disproportion are contraindications to VBAC. [19]

2.1.2 Global Epidemiology of Cesarean Section Delivery

Researchers from the WHO recently conducted an ecologic analysis of trends of CS delivery worldwide. [8] From the survey of 150 countries with national-level data on mode of delivery and live births, the authors estimated that the average rate of CS delivery globally in 2014 was 18.6% (range 6.0%-27.2%). This rate varied by region, with Latin America and the Caribbean region having the highest regional CS rate at 40.5%, largely influenced by the South American sub-region which had the highest rates of CS at 42.9%. North America and Oceania had CS rates of 32.3% and 31.1%, respectively, followed by Europe at 25%. Asia had a CS rate of 19.2%, and Africa had the lowest CS rate at 7.3%. Overall, the rate of CS delivery is estimated to have increased globally by 12.4% between 1990 and 2014, with the largest absolute increase seen in Latin America and the Caribbean, and Asia.[8]

2.1.2.1 National and Regional Estimates of Cesarean Section Prevalence in India

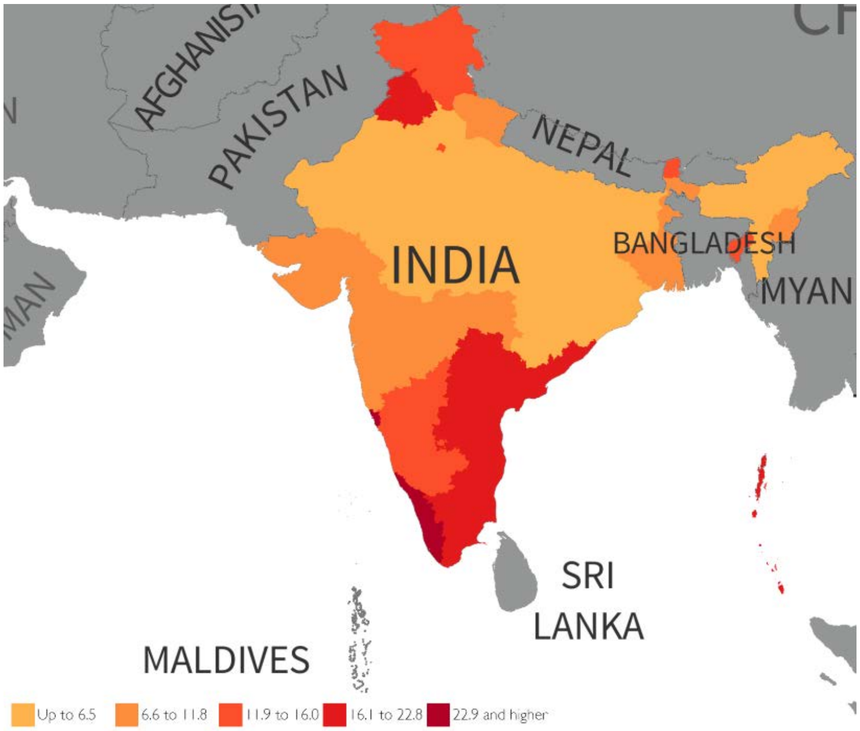
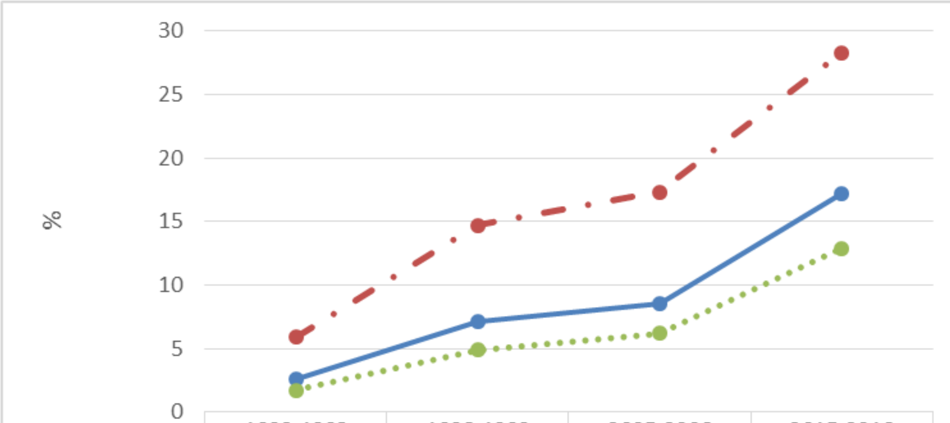


Figure 1 Percentage of live births in three years preceding the NFHS delivered by cesarean section

The national prevalence of CS in India has modestly increased over the past 25 years. According to data from the National Family Health Survey, the national CS rate in 1992-93 was 2.6% and rose to 17.2% in 2015-16. [23] [9] Figure 1 shows the regional differences in CS rates in 2005-06, and Appendix Table 20 shows the state-level increases in CS rates over the three NFHS surveys. Further, the increase in CS over time has been more pronounced in urban areas compared to rural areas (Figure 2).



	1992-1993	1998-1999	2005-2006	2015-2016
Total	2.6	7.1	8.5	17.2
Urban	5.9	14.7	17.3	28.3
Rural	1.7	4.9	6.2	12.9

Figure 2 Percentage of live births in three years preceding the NFHS delivered by cesarean section and place of residence

A survey of health institutions by the Indian Council of Medical Research found that the rate of CS at tertiary care hospitals increased modestly from 21.8% in 1993-1994 to 25.4% in 1998-1999. [24] The lowest and highest CS rates at individual institutions in 1993-1994 were 8.7% and 37.8%, compared to 9.1% and 47.0% in 1998-1999. Private hospitals tend to have higher rates as there are fewer medical practice regulations, including cost management and standard of care. [25]

The regional differences in CS prevalence have also been observed in previous research studies, although many were conducted over short time frames and may not reflect the most recent trends. A cross sectional, population based study in the southern state of Madras (Chennai) conducted by cluster sampling of 780 births between 1997 and 1999 found that the overall CS rate was 32.6%.[26] This rate varied by type of facility, with private health facilities having a CS rate of 47% and public health facilities at 20%. Another study in Chennai at a government hospital had a CS rate of 48.8% in 2013. [27] A retrospective study using data from a tertiary government hospital in South West India found that the proportion of CS increased from 20.2% of all deliveries in 2005 to 23.2% in 2009, while another study from 2015 in Western India had a CS rate of 29.2%. [28,29] A study using the National Family Health Survey data in the southern state of Kerala to assess how different variables are associated with CS delivery in that state found that the proportion of CS in the 1992-1993 survey was 12.8%, the second highest prevalence in the country at that time. [30] Table 2 summarizes the prevalence of CS in India by state and region.

Table 2 Select Studies of Cesarean Section Prevalence in India

AUTHOR, PUB. YEAR	LOCATION (STATE, REGION)	STUDY SETTING, DESIGN	N	CS PREVALENCE (STUDY PERIOD)	OTHER FINDINGS
Dhanapal et al, 2016 [27]	Tamil Nadu, South	Hospital based, Retrospective	7810	48.8% (2013)	15% of the CS were elective, 85% emergency
Pandya et al., 2015 [29]	Ahmedabad, West	Hospital based, Retrospective	500	29.2% (2015)	
Unnikrishnan et al., 2010 [28]	Karnataka, South	Hospital based, Retrospective	7543	23.3% (2009)	CS rate increased from 20.2% in 2005
Sreevidya et al, 2003 [26]	Tamil Nadu, South	Hospital based, Cross sectional	780	32.6% (1997-1999)	CS rate varied by health facility -20% in public sector, 38% in charitable sector, 47% in private sector
Kambo et al., 2002 [24]	Nationwide	30 medical colleges or teaching hospitals, Retrospective	206, 164	24.4% (1998-1999)	CS rate increased from 21.8% in 1993-1994
Padmadas et al., 2000[30]	Kerala, South	Statewide, Cross sectional	2021	12.8% (1992-1993)	

2.1.3 Review of Risk Factors for Cesarean Section Delivery Globally

2.1.3.1 Medical Indications

Abnormal labor progress, known as dystocia, is the most common medical indication for CS in nulliparous women.[19] A frequently reported form of dystocia is cephalo-pelvic disproportion (CPD), which causes obstructed labor and can be fatal for both mother and fetus if not intervened on operatively. In cases where dystocia is characterized by labor failing to progress, amniotomy (breaking of the amniotic sac) is performed. However, this can also affect fetal heart rate, and fetal distress is an indication for CS. Other indications for CS delivery include placenta previa, and active genital herpes. [31]

Previous CS, CPD, fetal malpresentation, and fetal distress were found to be the most common indications for CS delivery in a hospital based study in four South East Asian countries – Indonesia, Malaysia, Philippines, and Thailand. [32] These indications accounted for an overall CS rate of 27% (range 19-35 %) out of 9,550 pregnancies in 2005, with only 2.1% of the CS deliveries in one country attributed to maternal request. Similarly, previous CS, difficult labor, fetal distress, and breech presentation were found to be the most prevalent medical indications for CS delivery in a high parity population (mean gravidity of 4.6 ± 3.3) in a retrospective study of a large tertiary care hospital in Saudi Arabia. [33]

The most common indications for primary CS deliveries in an urban medical center in the US from 2003 to 2009 were non-reassuring fetal status, arrest of dilation or descent in labor, and multiple gestations. [34] Suspected macrosomia, pre-eclampsia, maternal request, and maternal-fetal conditions were also noted as contributing to the increase in primary CS in this prospective analysis. Even when maternal age and birthweight ≥4,500g was stable over the 7 year period, the CS rate increased by 73%.

Similar patterns of obstetric indications for CS pertaining to CPD, fetal malpresentation, or fetal distress have been found in other populations in Nepal [35], Ethiopia [36], and Thailand [37]. These similarities indicate the universal need for surgical intervention in labor and delivery in order to prevent adverse outcomes, including perinatal mortality. However, the definition of indications are not uniform across studies, and we are unable to ascertain the quality of medical care in each setting, adding to the difficulty of comparing of findings.

2.1.3.2 Maternal Characteristics

One suggestion for the increasing trend of CS deliveries in developed countries stems from increasing maternal age at first delivery. Ecker et al. found that in a sample of 3,715 term nulliparous women that delivered at Brigham and Women's Hospital in 1998, 43.1% of women 40 years old and older were delivered by CS compared to 11.6% of women who were 25 years old or younger (p-value for trend =0.001).[31] Older age in this nulliparous study population was also associated with increased labor induction, failure to progress in labor, and fetal distress. Age was also acknowledged as a contributing factor to the CS rate of 31.7% in Germany, where 22% of the women giving birth are over age 35.[38] There may be biological reasons for why advanced maternal age at first delivery is associated with additional risks for CS, including a higher propensity for fetal malpresentation and multiple gestation with increasing maternal age. In addition, uterine aging has been suggested to contribute to higher diagnoses of dystocia, leading to CS for indication. [31]

In addition to age as a significant demographic factor, there are racial and ethnic differences in CS rates. In the US, African American women are more likely to be delivered by CS compared to other ethnicities.[39] A retrospective cohort study using California inpatient data for 493,433 women found that African American women were significantly more likely to deliver by CS at a rate of 36.8%, compared to 32.7% for women of other races/ethnicities.[39] After adjusting for maternal and delivery admission characteristics, and hospital annual deliveries, African American women were significantly more likely to have primary and elective primary CSs (aOR 1.27, 95% CI 1.21-1.33 and 1.31, 95% CI 1.23-1.39, respectively). In contrast, American Indian women have been found to have the lowest CS rates of all US ethnic groups. [40] A study conducted using birth certificate data for American Indian women in New Mexico (n=3,654) found that the CS rate was low despite having similar risk factors for CS as found in the general population in the US, such as older maternal age and nulliparity. [40] Racial disparities in CS delivery may not have a biological basis. Rather, it may be a reflection of institutional practices and access to care as patients cluster by race in hospitals in which the same quality of care is given. [39] Race is also associated with factors such as socioeconomic class and insurance status, which can affect quality of treatment on account of biases in healthcare providers. [41]

Maternal anthropometrics have also been associated with CS rates. Maternal pre-pregnancy obesity has been identified as an independent factor that increases the likelihood for cesarean delivery. In a retrospective cohort study of 143,463 women who delivered at 19 hospitals in the US, as maternal body mass index (BMI) on admission increased so did primary CS rates. [42] Higher BMI was associated with dystocia or CPD for nulliparous and multiparous women, although non-reassuring fetal heart rate was not associated with increasing BMI. [42] In addition, short maternal height has also been found to be associated with CPD, and thus CS delivery. A retrospective study of 9,198 Thai women found that height of 145 cm or shorter increased the likelihood for obstructed labor. [43] This is because maternal height is correlated with pelvic size, thus women of shorter stature tend to have smaller pelvises and a higher likelihood for obstructed labor.

Some studies find a range of maternal characteristics that increase the likelihood for CS delivery. For example, a study in British Columbia, Canada, assessed indications of 1,302 nulliparous women with no apparent risk for CS and found that characteristics including advanced maternal age, shorter stature, and maternal perception of length of labor increased the likelihood of CS delivery. [44]

2.1.3.2.1 Vitamin D Deficiency

Studies have shown an association between vitamin D deficiency and increased risk of primary CS after adjusting for confounders, indicating the role of maternal nutrition in pregnancy. [45,46] The biological explanation for this is that the strength of pelvic muscles may be reduced when a woman is vitamin D deficient, and this would affect her ability to push and deliver a baby vaginally. [46] Vitamin D deficiency (defined as <30 nmol/L of circulating serum 25-hydroxyvitamin D (25(OH) D)) in a study of low income women in New Jersey, USA, was associated with an increased risk of prolonged labor in both primi and multipara after adjusting for age, parity, ethnicity, smoking, gestational age at entry to the study, and season at entry. [46]

2.1.3.2.1.1 Vitamin D Deficiency in Indian Women

Numerous studies have found high rates of vitamin D deficiency in populations across India in both urban and rural populations, and some consider vitamin D deficiency to be endemic.[47-51]

A multiethnic study in Singapore found that vitamin D inadequacy (defined as <75 nmol/L 25(OH) D) in Indian women was associated with a 2-fold increase in odds of emergency CS delivery (OR 2.41, 95% CI 1.01-5.73). [52] Conversely, a case control study in south India did not show an association between vitamin D deficiency (defined as <20 ng/mL 25(OH)D) and CS for dystocia as a primary or secondary indication after adjusting for maternal age, religion, BMI, SES, and infant birth weight (aOR 2.31, 95% CI 0.77-6.92). [53] However this study may have been underpowered to assess a difference in vitamin D deficiency between the cases and controls. They did find a significant association between higher BMI and CS after adjusting for confounders (aOR 1.31, 95% CI 1.13-1.52). The authors did not provide a rationale for adjusting for variables such as religion, age, and SES, which were not significantly associated with the outcome in bivariate analyses.

2.1.3.2.2 Maternal Perception

In the United States, a number of theories have been posited to explain the increase in CS rates in the 21st century. In a commentary by Howard Blanchette addressed to obstetricians practicing in the US, factors such as physician convenience and maternal request for elective primary CS were addressed.[54] He attributed maternal request to factors such as fear of labor pain and wanting to avoid pelvic floor damage, in addition to the perception that CS is safer for the fetus. The maternal perception of the safety of CS delivery was also suggested by researchers in Portugal, and may have contributed to the country's highest CS rate of 36.6% in 2009.[55]

Using 1998 birth certificate data in Taiwan, Lo found that while medical risk factors were associated with higher CS rates in clinics and hospitals, there was also an association between CS delivery and days considered auspicious, according to the Chinese lunar calendar. [56] This shows that maternal cultural beliefs can have an effect on planned CS rates, as can negative perceptions about pain and safety during delivery. [57] Belief in auspicious timing has also been attributed as one of the reasons for increases in CS deliveries in India. [58]

2.1.3.2.2.1 Maternal Perception of Mode of Delivery in India

Previous studies in India have assessed maternal perceptions of the birthing experience in general, looking at a range of factors including access to healthcare during pregnancy and at the time of delivery.[59-61] These have been conducted in rural settings where challenges persist in getting access to adequate obstetric care and home deliveries are commonly practiced. One qualitative study conducted with 32 rural participants in the state of Jharkhand found that women had negative perceptions about CS delivery and hospital-based procedures in general.[59] This is related to women reporting being ill-treated by hospital staff and thus preferring home deliveries by rural medical practitioners, where they could also receive support from family members.

Conversely, another study conducted in Calcutta used a questionnaire to assess the views on mode of delivery in 205 women receiving antenatal care at a hospital.[60] They found that over 70% of the women believed that CS delivery is safer for the infant compared to vaginal delivery. Similarly, a qualitative study with 22 rural women in the state of Tamil Nadu found that the high rate of CS deliveries in the sample, at 23% compared to the state-wide CS rate of 14% in Tamil Nadu, may be related to the positive perception of CS delivery relating to safety of the infant.[61]

To inform the design and interpretation of the dissertation research aims, a pilot study entitled “Maternal and Medical Provider Perceptions of Mode of Delivery in an Indian Population” was conducted in 2016 (report summary in Appendix). This study used mixed methods (focus group discussions and written questionnaire) to assess knowledge and perceptions of mode of delivery in a peri-urban Indian population in Telangana state.

2.1.3.3 Health Care

A cross-sectional study of hospital surveillance data from 2005-2011 in Bangladesh, India, and Nepal found that CS rates in 45,327 births varied by public and private facilities. [62] The overall CS delivery without medical indication was 18% in private facilities compared to 5% in public facilities After adjusting for year of delivery, maternal characteristics (age, education, household wealth), and pregnancy and delivery characteristics (antenatal care visits, parity, pregnancy complications, multiple birth), women in rural Bangladesh were 5.9 times more likely to have a CS delivery in private health facilities than in public health facilities (95% CI 5.2-6.8), while in urban India they were 1.2 times more likely (95% CI 1.1-1.4) and in rural Nepal they were 2.4 times more likely (95% CI 1.6-3.4).

Conversely, women in rural India were less likely to deliver by CS in private health facilities compared to public health facilities (aOR 0.5, 95% CI 0.3-0.7). [62] This study also found that high maternal education compared to no education was associated with increased CS delivery in rural Bangladesh (aOR for bachelor degree or higher 2.4, 95% CI 1.5-3.9) and in urban India (aOR for bachelor degree or higher 1.6, 95% CI 1.3-2.0). Furthermore, in these two locations the wealthiest household wealth quintile was associated with increased CS delivery compared to the poorest quintile (aOR rural Bangladesh 1.4, 95% CI 1.1-1.7, aOR urban India 1.5, 95% CI 1.3-1.8). However, the study was limited by incomplete knowledge about pre-pregnancy maternal factors.

2.1.3.3.1 Health care access in India

Health outcomes have improved in India over time. However, these are determined by social and demographic factors such as geography, caste, wealth, education, and gender. [63] According to findings in the 2005-2006 National Family Health Survey, 38.7% of women reported delivering their most recent birth in a health facility, and this varied by wealth quintiles, with those in the poorest quintile being six times less likely to deliver in a facility than those in the wealthiest quintile. [63] This may influence the trend that CS deliveries are higher in urban areas in India, where wealthier populations reside. Further, there is a difference in access to health care by geographic location, in that the number of beds in government hospitals in urban locations is more than double those in rural areas. [63]

An intervention program known as Janani Suraksha Yojana (JSY) has been implemented by the Indian Government to encourage all women to deliver at health facilities with skilled birth attendants.[64] The program provides cash incentives and support from a health worker. JSY has helped increase deliveries in health care facilities since its implementation in 2005 as it alleviated the cost of health care for poor families.

2.1.3.3.2 Physician's Perception

Few studies have been conducted assessing physicians' perception or preference of mode of delivery. One study in Ireland assessed whether obstetrician's personal preference for mode of delivery was associated with rates of CS delivery in their medical practice. [65] Out of the 165 respondents to their mail survey assessing responses to hypothetical pregnancy scenarios, 7% of the obstetricians reported that they would choose elective CS delivery for themselves or their partner for a cephalic, term, uncomplicated pregnancy, and 38% would choose elective CS delivery if the fetus had an estimated weight of 4.5 kg. The authors state that an association was found between obstetrician personal preference for elective CS and the CS delivery rate in their hospitals, yet statistical tests were not conducted to assess the validity of this association. This study was preceded by a similar survey on personal preference for mode of delivery conducted among 206 physicians in London, UK, in 1996. [66] Here, 17% of obstetricians reported opting for elective CS in an uncomplicated, term pregnancy for themselves or their partner, while 39% would opt for CS delivery if the fetus weighed an estimated 4 kg, and 68% if the weight was greater than 4.5 kg. Reasons cited by these obstetricians for hypothetically choosing elective CS delivery for an uncomplicated pregnancy included fear of perineal damage and concern about long-term effects on sexual function after vaginal delivery. [66]

In 2013 and 2014, researchers at the London School of Hygiene and Tropical Medicine conducted an online survey with obstetricians in countries around the world in order to assess their opinion of the optimal CS rate in general for all deliveries, as well as for various medical indications. [67] They found that the median optimal CS delivery rate recommended by 941 respondents was 20% of all deliveries (range 3-90%). Choice of optimal rates was significantly associated (Kruskal-Wallis p-value <0.05) with a number of factors, including the national CS delivery rate of the participant's country, whether they practiced at a public or private facility, and their facility's CS delivery rate. Obstetricians from countries with a national CS rate greater than 30%, those who worked at private facilities and facilities where the CS delivery rate was greater than 50% were more likely to report high optimal CS rates. The median optimal CS delivery rate of 20% suggested by the surveyed obstetricians is higher than the 5-15% range recommended by the WHO, and may indicate lack of consensus between practice and policy regarding CS delivery worldwide. [67] A different survey of 100 obstetricians in Turkey found that not only were a majority of this sample not in favor of performing trial of labor after cesarean (TOLAC), they acknowledged that the high CS rate (51.1% in 2014) was likely due in part to medical litigation concerns. [68]

2.1.3.4 Summary of Risk Factors for Cesarean Section Delivery

Table 3 presents a summary of findings on risk factors for CS delivery, demonstrating that the decision to perform CS delivery is multifactorial. Epidemiological studies have shown that medical indications continue to be a major factor for CS deliveries, in which case this is a lifesaving procedure. In addition, a range of maternal characteristics have been found to be associated with CS delivery, including physical attributes such as stature and weight, socio-demographic factors, age and race/ethnicity. Health care also affects mode of delivery, including the complex contribution of physician perception and medical practice. How these multiple factors collectively contribute to mode of delivery has seldom been studied. The impact of pre-pregnancy characteristics on mode of delivery and subsequent maternal and infant health outcomes is understudied.

Table 3 Summary of Select Studies on Risk Factors for Cesarean Section Delivery

RISK FACTOR CATEGORY	AUTHOR, YEAR	STUDY DESIGN	POPULATION	LOCATION	TIME PERIOD	FACTORS
MEDICAL INDICATION						
	Festin et al, 2009 [32]	Retrospective	9,550 pregnancies	Indonesia, Malaysia, Philippines, Thailand	2005	Previous CS, cephalo-pelvic disproportion, fetal malpresentation, fetal distress
	Al Rowaily et al, 2014 [33]	Retrospective	4,305 women	Saudi Arabia	2008-2011	Previous CS, difficult labor, fetal distress, and breech presentation
	Barber et al, 2011 [34]	Prospective	32, 443 primary pregnancies	US	2003-2009	Non-reassuring fetal status, arrest of dilation or descent in labor, and multiple gestations.
MATERNAL CHARACTERISTICS						
	Ecker et al, 2001 [31]	Retrospective	3,715 nullipara	US	1998	Older maternal age
	Huesch et al, 2015 [39]	Retrospective	493,433 women	US	2010	African American race
	Janssen et al, 2016 [44]	Secondary analysis of an RCT	1, 302 women	Canada	2001-2004	Advanced maternal age, shorter stature, and maternal perception of length of labor
	Kawatika et al [42]	Retrospective	143, 463 women	US	2002-2008	Increasing obesity class
	Scholl et al, 2012 [46]	Prospective	1,153 women	US	2001-2007	Vitamin D deficiency (25(OH)D < 37.5nmol/L)
	Loy et al, 2015 [52]	Prospective	940 women	Singapore	2009-2010	Vitamin D inadequacy (25OHD </=75nmol/L)
	Neuman et al, 2014 [62]	Cross-sectional	45, 327 births	Bangladesh, India, and Nepal	2005-2012	High maternal education, wealth
MATERNAL PERCEPTION						
	Blanchette, 2011 [54]	Commentary	-	US	2011	Maternal request
	Hug et al, 2008 [60]	Structured interviews	205 women	India	2002	Belief that CS delivery is safer for the infant
	Lo, 2003 [56]	Cross-sectional	215, 656 birth certificates	Taiwan	1998	Auspicious days
	McCourt et al, 2007 [57]	Systematic literature review	17 articles	International	2000-2005	Cultural influence, fear of pain

Table 3 - Continued

HEALTH CARE						
	Neuman et al, 2014 [62]	Cross-sectional	45, 327 births	Bangladesh, India, and Nepal	2005-2012	Private health facilities
	Mc Gurgan et al, 2001 [65]	Postal survey	165 obstetricians	Ireland	1999	Physician personal preference
	Al-Mufti et al, 1997 [66]	Postal survey	206 obstetricians	England	1996	Physician personal preference
	Cavallaro et al, 2016 [67]	Online survey	1,057 physicians	International	2013-2014	Practice at a private facility, national CS rate >30%
	Kucuk , 2017 [68]	Self-administered questionnaire	100 obstetricians	Turkey	2016	Fear of litigation

2.1.4 Adverse Outcomes Associated with Cesarean Section Delivery

2.1.4.1 Adverse Infant Outcomes

2.1.4.1.1 Mortality

While the under-five mortality rate worldwide has decreased by 53% since 1990, preventable child deaths are still a major concern in many countries. [69] The neonatal period, the first four weeks of life, has particularly been recognized as a vulnerable stage, and deaths during this time are likely correlated with maternal health care. [69]

The association between CS delivery and neonatal mortality has been explored in epidemiologic research studies. One study of national-level data from 46 countries found that neonatal mortality was increased in countries with CS rates of <15%. [70] The propensity score matched analysis adjusted for covariates including household wealth, antenatal care, maternal education, urban or rural residence, and a measure for gross domestic product per capita.

2.1.4.1.2 Hygiene Hypothesis

According to a theory known as the 'Hygiene Hypothesis', because CS delivery does not expose the infant to the mother's vaginal microflora they may not develop the same microbiota and immunity as infants born by vaginal delivery.[71] The exposure to bacteria from the mother's skin and hospital environment at birth instead of vaginal microbes such as *Lactobacilli* is thought to affect the infant's immune system development. This is because initiation of immunity begins in the intestinal tract, thus colonization by pathogenic bacteria may incorrectly prime the immune system and predispose the infant for immune associated health conditions. [72] In relation to this theory, studies have found CS delivery to be associated with an increased risk of the child developing conditions such as Celiac disease, allergic rhinitis, and asthma.[71]

2.1.4.2.3 Health Outcomes

Numerous studies have been conducted to assess the effect of mode of delivery on health outcomes from infancy through adulthood, including obesity, [73,74] autism spectrum disorders, [75] atopic diseases, [76] chronic immune diseases, [77] [78] gastrointestinal, [79-82] and respiratory disorders [76,83-87]. Appendix Table 21 summarizes the findings from these studies.

While majority of studies showing a positive association between mode of delivery and adverse infant outcomes have been conducted in the US, Europe, or Australia, few studies have been conducted in low or middle income settings. In one case, a longitudinal cohort study in India and Vietnam that used the child's caregiver's report of asthma or wheeze at 8 years of age found a higher rate of asthma in children born by CS delivery. [83] The likelihood of the outcome was doubled in both Indian children (OR 2.6, 95% CI 1.3-5.4) and Vietnamese children (OR 2.0, 95% CI 1.2-3.3) after adjusting for breastfeeding and a propensity score incorporating the variables wealth index, child's sex, parity, low birthweight at term, geographic location, cooking fuel, ownership of livestock, household smoking, maternal age, housing quality and household size.

Few studies have been conducted on short-term infant outcomes associated with mode of delivery, even though this is likely the most appropriate time period for assessing obstetric related outcomes since the infant has had little exposure to other environmental factors. One prospective cohort study conducted in Germany found that the likelihood for diarrhea in the first 12 months of life was higher in infants delivered by CS compared to those vaginally delivered. [80] They further decreased biasing the results by restricting their study sample to those who were exclusively breastfed. Another hospital-based study in Burma found a five-fold increased likelihood of diarrhea in neonates delivered by CS compared to those delivered vaginally. [82] However, this study did not conduct multivariable analysis to account for additional factors that may confound the association between mode of delivery and diarrhea.

2.1.4.2 Maternal Health Outcomes

In addition to adverse infant outcomes, a number of adverse maternal outcomes have been found to be associated with CS delivery. A multi-country WHO survey on delivery method and pregnancy outcomes in Asia found that non-medically indicated CSs were associated with an increased risk of maternal mortality and morbidity compared to spontaneous vaginal delivery. [5]

Other studies have found that CS delivery is associated with problems initiating breastfeeding, greater than 1L of blood loss, lacerations, hematoma, urinary tract infection, postpartum hysterectomy, and placental abnormalities such as placenta previa. [88-92]

In regards to subsequent pregnancy, studies have shown that primary CS is associated with a decreased likelihood of a subsequent pregnancy compared to primary spontaneous vaginal delivery, and ectopic pregnancy or still birth in subsequent pregnancy, but not miscarriage, or infertility. [93-96]

2.1.5 Conclusion

With the increasing rate of CS delivery globally, it will be important to evaluate the short and long term effects of mode of delivery in different populations, particularly those in low and middle income settings which have been understudied. It is also important to assess the role that multiple factors have on mode of delivery, in order to further help in making informed obstetric decisions and guide interventions to reduce unwarranted CS deliveries.

With an estimated population of 1.3 billion people in 2016, India is the second most populated country, only surpassed by China with 1.4 billion people. [97] India is also expected to lead in population growth from 2017 to 2050, eventually becoming the most populous nation in the world. [97] Analyzing CS trends and outcomes in India could be informative for other populations experiencing concurrent population increase and economic development.

This dissertation aims to assess factors associated with mode of delivery in a peri-urban Indian population, and will add to the knowledge gained from previous research studies by accounting for pre-pregnancy maternal and labor and delivery factors in our analyses. In addition, we account for pre-delivery factors associated with mode of delivery in our assessment of the adverse infant outcomes diarrhea and respiratory infection to reduce bias. Assessing short-term gastrointestinal and respiratory disease outcomes in infants allows us to test whether or not the 'Hygiene Hypothesis' is plausible in an Indian population, which has not previously been done.

Using national-level data, we will replicate these analyses, and additionally assess the effect of place of residence and socio-economic variables on mode of delivery. Furthermore, with the national data we will be sufficiently powered to assess an important but rare infant outcome: neonatal mortality. This will add to the sparse knowledge about whether mode of delivery affects mortality in low and middle income settings.

The research aims of this project will be accomplished using two data sets: the Longitudinal Indian Family hEalth (LIFE) study and the 2005-2006 National Family Health Study (NFHS-3).

2.2 THE LONGITUDINAL INDIAN FAMILY HEALTH STUDY

2.2.1 Original Study Design and Population

The Longitudinal Indian Family hEalth Study (LIFE) study was created in collaboration between the Science Health and Applied Research Education (SHARE) India Program and the University of Pittsburgh in 2009.[7] The Rural Effective Affordable Health Care (REACH) program, a translational program to improve maternal and child health and was established by SHARE India and MediCiti Institute of Medical Sciences (MIMS). REACH provides health education, immunizations, antenatal care, primary, and tertiary care for a population of 43,270 in 40 villages in the Ranga Reddy District on the northern outskirts of Hyderabad.

Inclusion criteria for enrollment in the LIFE study are 1) married women residing in an eligible village; and 2) age 15 to 35 years. [7] Exclusion criteria are: 1) residing in one of 14 villages with a highly transient population; 2) women who have undergone tubal ligation/hysterectomy/oophorectomy, or their husband has undergone vasectomy; 3) women using birth control; or 4) are currently pregnant beyond their first trimester. For all women in the cohort, questionnaires are administered at study enrollment, first trimester, third trimester, delivery (for women delivering at MIMS), 48 hours postpartum (for women delivering outside of MIMS) and one month postpartum. Table 4 presents the quantitative data collected from the study questionnaires at each follow-up time period. The study population includes all REACH villages except for two villages with a high proportion of transient residents.

Biological samples obtained at enrollment from each participant includes self-collected vaginal swabs, urine, and stool, and blood draw by study staff. [7] In addition, at enrollment physical measurements are taken for each participant, and a questionnaire regarding demographic characteristics is administered. Study follow-up after enrollment entails research staff contacting participants who are not already pregnant to determine if a pregnancy has occurred based on a missed menstrual cycle. A confirmatory urine test is performed if a woman reports that she missed her menstrual cycle, and if the test is positive she is scheduled for a first trimester study visit. The questionnaire administered at the first trimester visit collects information on reproductive history and ongoing health conditions. Another study visit occurs at the beginning of the third trimester of pregnancy, including a questionnaire assessing health conditions and environmental exposures. Any pregnancy loss that occurred since the first trimester visit is recorded on a separate questionnaire which ascertains the reason for the pregnancy loss.

Additional biological samples are collected at delivery if a study participant delivers at MIMS, including vaginal, urine, stool, and blood samples from the mother, and meconium, stool, cord blood samples from the infant, and a sample of the placenta. Chart abstraction of deliveries is conducted to collect information on any labor and delivery complications, mode of delivery, and details on infant health. This information is more complete for deliveries at MIMS than those outside of MIMS.

The first postpartum study visit occurs at one month, with a questionnaire assessing infant health in the neonatal period. The next follow-up visits occur at six month intervals until 24 months, then annually thereafter, with each visit assessing the health, growth and development of the child.

Table 4 LIFE Study Questionnaire Variables

Category	Variables	Time of Collection					
			Pregnancy		Delivery	Post-partum	
		Enroll.	1^{st} tri.	3^{rd} tri		1 month	6+ months
Maternal Characteristics							
Demographics	Age; caste/tribe; religion; education	X					
Occupation	Work outside of home; type of work; recent travel for work	X	X	X		X	X
Anthropometrics	Height, weight; waist circumference; hip circumference	X	X	X		X	X
Pregnancy	Health conditions during pregnancy; Pregnancy practices; Antenatal care		X	X			
Health	General health; recent health conditions; medication use; depression; dental health; physical activity	X	X	X		X	X
	Reproductive history;	X	X				
Delivery	Type of labor; complications; type of delivery; antenatal procedures, pregnancy loss				X		
Infant Measures and Outcomes							
Anthropometrics	Head circumference; length; arm circumference; abdominal circumference; chest circumference; weight;				X	X	X
Health	Ailments since delivery; health care; weight gain; breathing difficulty; feeding patterns; immunization					X	X
Development	Motor skills; mental assessment; social and emotional						X
Covariates							
Environment	Cooking; water sources, pesticide exposure; cigarette/bidi exposure; sanitation	X	X	X		X	X
Breastfeeding	Breastfeeding initiation; Ever breastfed infant				X	X	X

2.3 THE NATIONAL FAMILY HEALTH SURVEY

The National Family Health Survey (NFHS) is part of the Demographic and Health Surveys (DHS) that are conducted to assess maternal and child health in a variety of countries. [98] Surveys are conducted through a collaboration between the Indian Ministry of Health and the International Institute for Population Sciences. The first NFHS was conducted in 1992-1993, the second in 1998-1999, and the most recent survey with available data was conducted in 2005-2006, while data compilation for the 2015 -2016 survey is ongoing. Cleaned datasets are available upon request from the DHS program website. [99]

2.3.1 Data Collection

All NFHS surveys included women ages 15 to 49 years, and collected information on demographics, anthropometrics, receipt of antenatal care, health during pregnancy, and reproductive history. [98] Postpartum variables include breastfeeding practices, whether the child received immunizations, and whether they had any illnesses.

Data for the 2005-2006 NFHS was collected between November 2005 and August 2006 in all 29 states on India. [100] Using the national Primary Census Abstract as the sampling frame, two-stage and three-stage sampling designs were conducted to select survey participants in urban and rural areas. [100]

2.3.2 Reliability of NFHS Data to Assess Cesarean Section Delivery Rates

CS data in the NFHS is obtained by self-report from the survey respondent in the Woman's Questionnaire. The question asked by a trained interviewer is "Was (Child's Name) delivered by caesarean section?", with a dichotomous 'Yes/No' response. The numerator of this question is all positive responses, and the denominator is all live births in the last five years, for up to six children per woman.

An assessment of the reliability of DHS data for estimating national CS rates compared to aggregated health facility data found that in six countries the CS rate reported by DHS was higher than the rates reported by health facilities. [101] Despite the discrepancies, the 95% confidence interval for the estimates from DHS data included the health facility estimates. Overall the authors concluded that CS rates obtained from DHS may not be precise enough to determine trends, but are sufficient for global and national monitoring.

Noted issues with using DHS data include double-counting CS for multiple births, inflating the numerator, and reports of delivery by CS even when the delivery was not reported to have occurred in a health facility. Correcting data by removing observations where CS deliveries are reported outside of health facilities is recommended for better assessment of national CS rates using DHS data. [102]

3.0 MANUSCRIPT 1: FACTORS ASSOCIATED WITH MODE OF DELIVERY IN A PERI-URBAN INDIAN POPULATION

3.1 ABSTRACT

Objective: To evaluate which maternal factors differ by mode of delivery in a peri-urban Indian population.

Methods: Multivariable modified Poisson regression was used to model factors associated with cesarean compared to vaginal delivery in a prospective study in Telangana State, India. Adjusted relative risks and 95% confidence intervals are presented.

Results: Among 1,164 singleton births, 46% were delivered by cesarean. In multiparous women (n=931), prior twin delivery (4.2, 3.2-5.5), diagnosis of hypertension (2.4, 1.7-3.3), or pre-eclampsia (3.4, 2.5-4.7) in a prior pregnancy independently increased the risk of cesarean. Overweight/obesity (1.5, 1.2-3.9), intrauterine growth restriction (2.5, 1.6-3.8), non-reassuring fetal heart rate (2.2, 1.3-3.7), cephalo-pelvic disproportion (CPD) (3.1, 2.0-4.8), and breech position (2.2, 1.2-3.9) also increased the cesarean risk. In a sub-group of 674 multipara, for whom previous delivery records were available, prior cesarean delivery was a major factor (4.2, 3.2-5.6). Among nulliparous women (n=233), CPD (1.9, 1.2-3.0), a composite of any labor complications (2.9, 1.8-4.9), and breech position (3.4, 1.9-6.2) increased the risk of cesarean.

Conclusion: The high rate of cesarean delivery in this peri-urban Indian population is attributed to maternal differences in history of complications in prior pregnancies, history of prior cesarean, pre-pregnancy BMI, and medical indications at delivery.

3.2 INTRODUCTION

The rate of cesarean section delivery is increasing globally, yet has not coincided with an improvement in maternal and infant outcomes.[8] Further, cesarean delivery without medical indication is associated with adverse outcomes compared to spontaneous vaginal delivery. [2,5] In light of this, it is important to identify modifiable factors associated with cesarean deliveries in order to guide public health programs to reduce the rate of cesareans.

In India, approximately 17.2% of all births are delivered by cesarean. [9] This rate differs by geographic location and type of health care facility, ranging from 9.3% in rural public hospitals to 44.8% in urban private hospitals. [9] Between the dichotomy of rural and urban are populations residing in 'peri-urban' areas which have their own social and economic environments that may influence health outcomes, yet are understudied in relation to mode of delivery. [103]

Globally, women who deliver by cesarean have been found to differ from women who deliver vaginally in characteristics such as pre-pregnancy obesity, parity, stature, and prior cesarean delivery. [14,31,44,104] Other characteristics pertain to medical indications for cesarean that that arise during labor and delivery, including failure to progress in labor, dystocia, and fetal malpresentation. [31] The purpose of this analytic study is to evaluate which maternal factors are associated with mode of delivery in a peri-urban, southern Indian population with a high cesarean delivery rate.

3.3 METHODS

The Longitudinal Indian Family hEalth (LIFE) study is a prospective cohort study of reproductive aged women residing in a peri-urban area in Telangana State, India, outside of Hyderabad. Details of the LIFE study design have been previously described. [7] Briefly, the LIFE study was established to assess the effect of the maternal environment on birth outcomes and child development. Informed consent was obtained and the overall research protocol was approved by the SHARE INDIA/ MediCiti Institute of Medical Sciences Ethics committee. 1,227 women were enrolled pre-conception (80%) or in the first trimester of pregnancy (20%) between October 2009 and August 2011. The study is based at the MediCiti Institute of Medical Sciences (MIMS), a private hospital and health sciences college. Maternal demographic data were collected at enrollment, health assessments were conducted in the first and third trimesters of pregnancy, and details from labor and delivery were abstracted from medical records.

We analyzed data from 1,164 singleton births which occurred between March 2010 and December 2015. The primary outcome in this analysis was mode of delivery as indicated on the LIFE study labor and delivery abstraction form. Vaginal deliveries included spontaneous vaginal deliveries (n=586), vaginal deliveries with forceps assist (n=39), vaginal deliveries with vacuum assist (n=2), or vaginal deliveries with breech extraction (n=4).

Predictor variables were obtained by anthropometric assessments, self-report on enrollment questionnaires, first and third trimester questionnaires, and from labor and delivery abstraction. These variables were selected a priori and were categorized into six groups: *Demographics* (religion, caste/tribe, age at delivery, education, occupation), *Reproductive history* (parity, number of live births, age at first pregnancy, prior delivery of twins, diagnosis of gestational diabetes, hypertension, preeclampsia, or anemia in a prior pregnancy), *Anthropometrics* (body mass index (BMI) using the World Health Organization (WHO) recommended cut-off points for public health action in Asian populations [105] -- Underweight : ≤18.49 kg/m^2, Normal: 18.5 - 22.99 kg/m^2, and Overweight/obese : ≥23.0 kg/m^2), *Antenatal care* (any ANC visits with a health care professional, number of ANC visits), *Prenatal Health* (abdominal pain with fever, vaginal bleeding, abnormal vaginal discharge, and/or pain during urination in third trimester, nausea in first and/or third trimester, diagnosis of any health conditions in third trimester, composite prenatal complications, intrauterine growth restriction (IUGR)), *Labor and Delivery* (private or public health care facility, composite labor complications, non-reassuring heart rate pattern, cephalo-pelvic disproportion, fetal position, and shoulder dystocia).

Maternal prenatal and labor complications recorded on the labor and delivery abstraction form were grouped into composite variables measuring report of one or more prenatal complications, or one or more labor complications (Box 1). The fetal indications intrauterine growth restriction (diagnosed prenatally by ultrasound biometry or fetal Doppler), cephalo-pelvic disproportion (diagnosed by clinical pelvimetry using Muller-Munro Kerr's method), and non-reassuring fetal heart rate were examined as individual predictors.

Proportions of each maternal factor were calculated to characterize all births by mode of delivery (vaginal vs cesarean). Unadjusted risk ratios and 95% confidence intervals (CI) of each factor predicting mode of delivery were obtained with bivariate analyses using modified Poisson regression with robust error variance.[106] This method also accounts for women with more than one pregnancy by clustering on participant ID. The predictors found to be statistically significant in the bivariate analyses were included in a backward stepwise regression model. A multivariable modified Poisson regression model with the variables selected into the model provided adjusted risk ratios (aRR) and 95% CI. We conducted complete case analysis using available data on predictor variables. Missing data mostly occurred in labor and delivery variables from deliveries outside of MIMS.

We conducted the multivariable analysis by parity, multiparous or nulliparous (those who reported not having a previous pregnancy at the first trimester visit), to minimize possible residual confounding by reproductive history. Further, in order to assess the effect of previous lower segment cesarean delivery, which was recorded in labor and delivery abstraction records only for MIMS deliveries, we repeated the analysis in births to multipara at MIMS only (n=674). All analyses were conducted using SAS 9.3 (SAS Institute, Cary, NC) and STATA 12 (StataCorp, College Station, TX).

3.4 RESULTS

The overall rate of cesarean delivery was 45.8%. By parity, 45.6% of the 931 births to multipara and 46.4% of 233 births to nullipara were delivered by cesarean. 60% of all cesarean deliveries were recorded as emergency cesareans (25% of all births).

For all 1,164 births, women who delivered by cesarean reported higher levels of education compared to women who delivered vaginally (Table 5). More women who delivered by cesarean were older than 25 years at their first pregnancy (including pregnancies before enrollment in LIFE), had a prior delivery of twins, and had been diagnosed with gestational diabetes, hypertension, pre-eclampsia, or anemia in a prior pregnancy. More women who delivered by cesarean were in the overweight/obese BMI category (≥23.0 kg/m2 using the WHO Asian BMI cut-offs), and had 5 or more ANC visits. More women who delivered by cesarean had one or more prenatal complications, and IUGR. Similarly, more women who delivered by cesarean had one or more labor complications measured by a composite variable, cephalic disproportion (CPD), non-reassuring fetal heart rate pattern, and the fetus in breech or transverse position. More cesarean deliveries occurred at MIMS or other private health care facilities compared with public health care facilities.

In the multivariable regression analysis for multiparous women (Table 6), reproductive history factors independently associated with an increased risk of cesarean delivery include prior delivery of twins (aRR 4.2, 95% CI 3.2-5.5), or diagnosis of hypertension (aRR 2.4, 95% CI 1.7-3.3), or pre-eclampsia (aRR 3.4, 95% CI 2.5-4.7) in a prior pregnancy. Being categorized as overweight/obese (≥23.0 kg/m^2, 16% of multipara) compared to normal (18.5-22.99 kg/m^2) also independently increased the risk of cesarean delivery (aRR 1.5, 95% CI 1.2-3.9). IUGR (aRR 2.5, 95% CI 1.6-3.8), non-reassuring fetal heart rate pattern (aRR 2.2, 95% CI 1.3-3.7), CPD (aRR 3.1, 95% CI 2.0-4.8), and a fetus in breech position compared to vertex position (aRR 2.2, 95% CI 1.2-3.9) were independently associated with an increased risk of cesarean delivery.

In the multivariable regression analysis for nulliparous women, one or more labor complications at delivery (aRR 2.9, 95% CI 1.8-4.9), CPD (1.9, 95% CI 1.2-3.0), or a fetus in breech position compared to vertex position (aRR 3.4, 95% CI 1.9-6.2) independently increased the risk of cesarean delivery (Table 6).

In the sub-analysis of 674 deliveries at MIMS to multipara only, previous cesarean increased the risk of cesarean four-fold in the multivariable model (aRR 4.2, 95% CI 3.2-5.6) (Table 7). In addition, prior delivery of twins (aRR 1.4, 95% CI 1.1-1.9), diagnosis of hypertension (aRR 1.4, 95% CI 1.0-2.0) or pre-eclampsia (aRR 3.5, 95% CI 2.1-5.7) in a prior pregnancy, and overweight/obesity (aRR 1.4, 95%CI 1.0-1.9) independently increased the risk of cesarean. Further, prenatal complications (aRR 1.3, 95% CI 1.0-1.8), one or more labor complications (aRR 1.5, 95% CI 1.0-2.3), non-reassuring fetal heart rate (aRR 2.3, 95% CI 1.3-4.1), and a fetus in breech position compared to vertex position (aRR 2.6, 95% CI 1.4-5.0), were independently associated with an increased risk of cesarean delivery.

3.5 DISCUSSION

In this analysis of 1,164 births in a peri-urban Indian population, in which the rate of cesarean delivery is 46%, we identified differences in maternal factors by mode of delivery. Our findings from the LIFE study suggest that reproductive history, pre-pregnancy BMI, prenatal health complications, and labor and delivery factors independently increase the risk for cesarean delivery. Among multiparous women, despite the rarity of some reproductive history factors, prior delivery of twins and prior pregnancy complications independently increased the likelihood of cesarean delivery, as did pre-pregnancy overweight/obesity. Furthermore, IUGR and fetal complications during delivery increased the risk of cesarean in multiparous women. In the subgroup of multipara that delivered at MIMS, previous cesarean delivery increased the risk of cesarean four fold after accounting for reproductive history, BMI, and labor and delivery factors, which were still statistically significant in the multivariable model. Among nulliparous women, as in multiparous women, labor and delivery complications increased the risk of cesarean delivery.

The finding that report of prior cesarean delivery is a major predictor of cesarean in subsequent deliveries in multiparous women is consistent with previous studies. MacDorman et al. posit that the rise in repeat cesarean deliveries after 1996 in the United States is in part attributed to a decrease in the obstetric practice of vaginal birth after cesarean (VBAC), coupled with an increase in primary cesarean deliveries. [14]

Higher maternal BMI was associated with an increased risk of cesarean delivery in multivariable models for multiparous women, and was borderline statistically significant in the multivariable model for nulliparous women. This is consistent with other research showing the likelihood of primary cesarean delivery is increased in women with pre-pregnancy obesity compared to normal weight women. [14,42] Obese women have been observed to have prolonged duration of labor compared to normal weight women. [42] Although pre-pregnancy obesity is not common in our study population (median BMI is 19.3 kg/cm2), the modest relationship between higher BMI and cesarean delivery indicates that pre-pregnancy weight is a potential target for intervention.

We found that medical indications during labor and delivery increased the risk of cesarean delivery, particularly emergency cesarean, which is consistent with other studies in Asia. [5,107] A cross-sectional study conducted at a government hospital in Hyderabad found that women who experienced hypertensive disorders, fetal distress, and fetal breech presentation had a higher rate of cesarean deliveries, and that 60% of cesarean deliveries were emergency. [107] Cephalo-pelvic disproportion is a common form of obstruction of labor and is a medical indication for cesarean delivery to avert maternal or infant mortality. [19] This might also be related to maternal stature, as the average height in this population is 152 cm (5ft). Fetal distress in the form of non-reassuring fetal heart rate pattern is also a medical indication for cesarean delivery to prevent perinatal mortality. Lastly, fetal breech position is also a medical indication for cesarean delivery, and cesarean delivery in breech pregnancies has been found to be protective against perinatal mortality. [5]

The high cesarean delivery rate in this peri-urban population reflects the trend in Telangana State. An estimated 58% of births in Telangana State are delivered by cesarean, according to data from the 2015-2016 India National Family Health Survey (NFHS-4), ranging from 40.6% in public hospitals to 74.9% in private hospitals.[108] While the estimated cesarean rate has increased nationally in India, from 8.5% in 2005 to 17.2% a decade later, the cesarean rate in Telangana State in comparison to the national cesarean rate is alarming. [9,100] Our study findings suggest that the cesarean delivery rate in peri-urban areas falls between the rates of rural and urban areas.

Suggestions for the rise in cesarean deliveries in India include reasons such as the greater uptake of institutional deliveries overall, physician convenience in part due to an imbalance in the ratio of obstetricians to patients, and financial gain for cesarean deliveries in private sector hospitals. [25,109] In addition, cultural factors have been suggested to play a role in the high cesarean rate; such as choice of a birth date due to belief in astrological auspicious days, and increasing preference for medicalized births.[58] Further investigation is needed to elucidate the cause of the high cesarean rates in India, which exceed the WHO recommendation of cesarean deliveries to not surpass 15% of births within each region. [1] Other countries considered emerging global economies have high cesarean rates, likely corresponding with improved access to advanced health services in the general population. For example, the estimated national cesarean rates in Brazil and China are 39.3% and 53% of births, respectively.[110,111]

Strengths of our study include our large sample size and population based design, which increases external generalizability of the findings to similar populations in India and other peri-urban settings. Secondly, we were able to separate analysis by parity, further distinguishing the differences by mode of delivery in these two subgroups. Lastly, as labor and delivery data were abstracted from hospital records, there is a lower chance of misclassification of the outcome.

We acknowledge that there are limitations to our study. Some predictors are obtained by self-report, and therefore there could be misclassification of exposures due to recall bias. Additionally, not all women in the study deliver at MIMS, the research site, and the quality of labor and delivery data is not as complete for women who deliver elsewhere. As 72% of the study cohort delivered at MIMS, we were still able to conduct analysis within the larger subgroup of deliveries at MIMS to ascertain the effect of prior cesarean delivery, an important predictor for mode of delivery. As this is a secondary data analysis, we are unable to assess the influence of other predictors which may be associated with high cesarean rates, such as maternal request, physician preference of cesarean, and the aforementioned cultural factors.

In conclusion, women in a peri-urban Indian population who deliver by cesarean differed in reproductive history, pre-pregnancy BMI, prenatal, and labor and delivery factors compared to women who delivered vaginally. Medical indications contributed to the high rate of cesarean deliveries in both multiparous and nulliparous women. As the rate of primary cesarean was high, and as history of cesarean was strongly predictive of repeat cesarean, strategies to prevent primary cesarean may be the most effective intervention to decrease the overall cesarean rate in this population. Further studies are needed to elucidate causes of high cesarean delivery in this population and in Telangana State, and to identify modifiable factors for non-medically indicated cesarean deliveries.

3.6 FIGURE AND TABLES

Prenatal complications
Fetal growth
- Intrauterine Growth Restriction (n=18)

Composite Prenatal Complications
- Preeclampsia (n=48)
- Pre-existing hypertension (n=7)
- Pregnancy Induced Hypertension (without protein in urine) (n=42)
- Oligohydramnios (n=51)
- Polyhydramnios (n=12)
- Gestational diabetes (n=13)
- Placenta previa (n=2)
- Preterm labor (n=48)
- Other significant vaginal bleeding (n=3)

Labor complications
Fetal conditions
- Cephalo-Pelvic Disproportion (CPD) (n=98)
- Non-reassuring fetal heart rate pattern (n=47)

Composite Labor Complications
- Abruption (n=5)
- Maternal hemorrhage (n=7)
- Cord prolapsed (n=2)
- Maternal fever (n=4)
- Arrest of labor (n=8)
- Hypertension (without protein in urine) (n=5)
- Hypotension (n=2)

Figure 3 Prenatal and Labor Complications Abstracted from Labor and Delivery Records in the LIFE study

Table 5 Characteristics of all Deliveries in the Longitudinal Indian Family hEalth (LIFE) Study from 2010-2015, by Mode of Delivery

Characteristic	Vaginal Delivery n (%)[a] N= 631	Cesarean Delivery n (%)[a] N= 533
Demographics		
Religion		
Hindu	558 (88.4)	478 (89.7)
Muslim	55 (8.7)	31 (5.8)
Christian	18 (2.9)	24 (4.5)
Caste and tribe		
Scheduled caste	126 (20.0)	116 (21.8)
Scheduled tribe	53 (8.4)	44 (8.3)
Backward caste	349 (55.3)	302 (56.7)
None of the above	103 (16.3)	71 (13.3)
Age at delivery (years)		
≤19	69 (10.9)	43 (8.1)
20-24	407 (64.5)	331 (62.1)
25+	155 (24.6)	159 (29.8)
***Level of education** [b]		
None	107 (17.0)	65 (12.2)
Primary/Middle School	172 (27.3)	123 (23.1)
Secondary School	307 (48.6)	286 (53.7)
Higher education	45 (7.1)	59 (11.1)
Works outside the home	141 (22.3)	128 (24.0)
Reproductive history [c]		
Parity		
Multiparous	506 (80.2)	425 (79.7)
Nulliparous	125 (19.8)	108 (20.3)
Total number of live births		
0	30 (6.4)	25 (6.6)
1	299 (63.8)	262 (69.5)
≥2	140 (29.8)	90 (23.9)
***Age at first pregnancy (years)**		
≤19	194 (41.4)	128 (33.9)
20-24	260 (55.4)	225 (59.7)
25+	15 (3.2)	24 (6.4)
***Prior delivery of twins**	0 (0)	4 (0.87)
***Diagnosis of gestational diabetes in prior pregnancy**	2 (0.4)	8 (2.1)
*** Diagnosis of hypertension in prior pregnancy**	15 (3.2)	39 (10.4)
Diagnosis of Pre-eclampsia in prior pregnancy	1 (0.2)	4 (1.1)
***Diagnosis of Anemia in prior pregnancy**	21 (4.5)	29 (7.7)
Repeat cesarean (multiparous deliveries at MIMS)	0 (0)	109 (40.0)
Anthropometrics		
***Body Mass Index- WHO Asian Cut-off points**		
Underweight (≤18.49 kg/m^2)	274 (43.4)	174 (32.6)
Normal (18.5 - 22.99 kg/m^2)	288 (45.6)	236 (44.3)
Overweight/obese (≥23.0 kg/m^2)	69 (10.9)	123 (23.1)

Table 5 - Continued

Antenatal care		
Attended an ANC visit with a health care professional	580 (99.3)	497 (98.6)
***Number of ANC visits reported at third trimester**		
<5	198 (34.2)	131 (26.4)
≥5	381 (65.8)	366 (73.6)
Prenatal Health		
Experience of lower abdominal pain with fever, vaginal bleeding, abnormal vaginal discharge, and/or pain during urination	23 (3.9)	20 (4.0)
Experiencing nausea and/or vomiting in first trimester	262 (44.1)	243 (50.1)
Experiencing nausea and/or vomiting in third trimester	161 (27.2)	128 (25.3)
Diagnosed with any health conditions in third trimester [d]	111 (18.7)	115 (22.8)
***Composite prenatal complications** [e]	133 (28.6)	150 (40.8)
***Intrauterine Growth Restriction**	6 (0.9)	12 (2.2)
Labor and Delivery		
***Delivered at MIMS or other private health facility**	567 (92.6)	516 (96.8)
***Composite labor complications** [f]	57 (9.2)	74 (17.5)
***Non-reassuring fetal heart rate pattern**	12 (1.9)	35 (6.6)
***Cephalo-Pelvic Disproportion (CPD)**	1 (0.2)	97 (18.2)
***Fetal position**		
Vertex	407 (98.8)	297 (94.9)
Breech	5 (1.2)	15 (4.8)
Transverse	0	1 (0.3)
Shoulder Dystocia	1 (0.2)	0 (0)

[a] Displaying column percent

[b] Level of education: Primary/Middle school: ≤ Grade 7; Secondary school: Grades 8-12; Higher education: ≥ Grade 13

[c] Reproductive history missing for n=322

[d] Health conditions diagnosed in third trimester including 1 or more of the following: sugar disease, high blood pressure, preeclampsia, feet swelling, face swelling, contractions, sore throat, anemia, genital sores, abnormal vaginal discharge, diarrhea, jaundice, burning on urination, goiter, any other condition

[e] Composite prenatal complications includes 1 or more of the following: Preeclampsia, Gestational diabetes, Pre-existing hypertension, Pregnancy Induced Hypertension (without protein in urine), Placenta previa, Other significant vaginal bleeding, Oligohydramnios, Polyhydramnios, Preterm labor

[f] Composite labor complications includes 1 or more of the following: Hypertension (without protein in urine), Hypotension, Pre-Eclampsia, Maternal fever, Arrest of labor, Cord prolapsed, Abruption, Maternal hemorrhage

*Statistical significant difference by mode of delivery determined by χ^2 test (p-value <0.05)

Table 6 Crude and Adjusted Risk Ratios Predicting Risk of Caesarean vs Vaginal Delivery in the 2010-2015 LIFE Study Deliveries, by Parity

	Multipara (n=931)		Nullipara (n=233)	
Characteristic	**Unadjusted RR (95% CI)**	**Adjusted RR (95% CI)**	**Unadjusted RR (95% CI)**	**Adjusted RR (95% CI)**
Demographics				
Age at delivery (years)				-
≤19	**0.6 (0.4-1.0)**	-	1.1 (0.8-1.5)	
20-24	Ref.		Ref.	
25+	1.1 (0.9-1.3)		**1.5 (1.1-2.2)**	
Level of education			-	-
None	Ref.	-		
Primary/Middle School	1.1 (0.8-1.4)			
Secondary School	1.2 (1.0-1.6)			
Higher education	**1.5 (1.1-2.0)**			
Reproductive history				
Age at first pregnancy (years)			-	-
≤19	0.9 (0.7-1.0)	-		
20-24	Ref.			
25+	**1.3 (1.0-1.7)**			
Prior delivery of twins	**2.1 (1.9-2.2)**	**4.2 (3.2-5.5)**	-	-
Diagnosis of Gestational diabetes in prior pregnancy	**1.8 (1.3-2.5)**	-	-	-
Diagnosis of hypertension in prior pregnancy	**1.7 (1.4-2.0)**	**2.4 (1.7-3.3)**	-	-
Diagnosis of Pre-eclampsia in prior pregnancy	**1.8 (1.2-2.8)**	**3.4 (2.5-4.7)**	-	-
Diagnosis of Anemia in prior pregnancy	**1.3 (1.0-1.7)**	-	-	-
Anthropometrics				
Body Mass Index				
Underweight (≤18.49 kg/m^2)	0.9 (0.8-1.1)	0.9 (0.6-1.3)	**0.7 (0.5-1.0)**	1.3 (0.7-2.4)
Normal (18.5 - 22.99 kg/m^2)	Ref.	Ref.	Ref.	Ref.
Overweight/obese (≥23.0 kg/m^2)	**1.5 (1.3-1.8)**	**1.5 (1.2-3.9)**	1.1 (0.8-1.6)	1.7 (0.96-4.9)
Antenatal Care				
≥5 ANC visits	**1.2 (1.0-1.4)**	-	-	-
Prenatal Health				
Composite prenatal complications [a]	**1.3 (1.1-1.6)**	**-**	**1.4 (1.0-2.1)**	-
Intrauterine Growth Restriction	**1.6 (1.2-2.2)**	**2.5 (1.6-3.8)**	**-**	**-**
Labor and Delivery				
Delivered at MIMS or other private health facility	**1.8 (1.1-2.8)**	-	**-**	-
Composite labor complications [b]	**1.3(1.0-1.6)**	1.2 (0.8-1.8)	**2.0 (1.5-2.6)**	**2.9 (1.8-4.9)**
Non-reassuring fetal heart rate pattern	**1.6 (1.3-2.0)**	**2.2 (1.3-3.7)**	**1.8 (1.3-2.4)**	1.4 (0.8-2.2)
Cephalo-Pelvic Disproportion	**2.4 (2.2-2.6)**	**3.1 (2.0-4.8)**	**2.4 (2.0-2.8)**	**1.9 (1.2-3.0)**
Fetal position				
Vertex	Ref.	Ref.	Ref.	Ref.
Breech	**1.7 (1.2-2.4)**	**2.2 (1.2-3.9)**	**2.0 (1.3-3.1)**	**3.4 (1.9-6.2)**
Transverse	**2.3 (2.1-2.5)**	-	-	-

[a] Composite prenatal complications includes 1 or more of the following: Preeclampsia, Gestational diabetes, Pre-existing hypertension, Pregnancy Induced Hypertension (without protein in urine), Placenta previa, Other significant vaginal bleeding, Oligohydramnios, Polyhydramnios, Preterm labor

[b] Composite labor complications includes 1 or more of the following: Hypertension (without protein in urine), Hypotension, Pre-Eclampsia, Maternal fever, Arrest of labor, Cord prolapsed, Abruption, Maternal hemorrhage

Table 7 Crude and Adjusted Risk Ratios Predicting Risk of Caesarean vs Vaginal Delivery in the 2010-2015 LIFE Study Deliveries to Multipara at MIMS

	Multipara (n=674)	
Characteristic	**Unadjusted RR (95% CI)**	**Adjusted RR (95% CI)**
Demographics		
Age at delivery (years)		
≤19	**0.5 (0.2-0.9)**	-
20-24	Ref.	
25+	1.1 (0.9-1.3)	
Reproductive history		
Prior delivery of twins	**2.2 (2.0-2.4)**	**1.4 (1.1-1.9)**
Diagnosis of Gestational diabetes in prior pregnancy	**1.7 (1.1-2.6)**	-
Diagnosis of hypertension in prior pregnancy	**1.8 (1.5-2.2)**	**1.4 (1.0-2.0)**
Diagnosis of Pre-eclampsia in prior pregnancy	**2.3 (2.1-2.5)**	**3.5 (2.1-5.7)**
Previous lower segment CS	**2.9 (2.6-3.3)**	**4.2 (3.2-5.6)**
Anthropometrics		
Body Mass Index		
Underweight (≤18.49 kg/m^2)	1.0 (0.7-1.2)	1.0 (0.7-1.3)
Normal (18.5 - 22.99 kg/m^2)	Ref.	Ref.
Overweight/obese (≥23.0 kg/m^2)	**1.6 (1.3-2.0)**	**1.4 (1.0-1.9)**
Prenatal Health		
Composite prenatal complications [a]	**1.3 (1.1-1.6)**	**1.3 (1.0-1.7)**
Intrauterine Growth Restriction	**1.7 (1.2-2.3)**	**-**
Labor and Delivery		
Composite labor complications [b]	**1.5(1.1-1.9)**	**1.5 (1.0-2.3)**
Non-reassuring fetal heart rate pattern	**1.7 (1.3-2.1)**	**2.3 (1.3-4.1)**
Cephalo-Pelvic Disproportion	**2.6 (2.4-2.9)**	0.9 (0.5-1.4)
Fetal position		
Vertex	Ref.	Ref.
Breech	**1.7 (1.2-2.4)**	**2.6 (1.4-5.0)**
Transverse	**2.3 (2.1-2.5)**	-

[a] Composite prenatal complications includes 1 or more of the following: Preeclampsia, Gestational diabetes, Pre-existing hypertension, Pregnancy Induced Hypertension (without protein in urine), Placenta previa, Other significant vaginal bleeding, Oligohydramnios, Polyhydramnios, Preterm labor

[b] Composite labor complications includes 1 or more of the following: Hypertension (without protein in urine), Hypotension, Pre-Eclampsia, Maternal fever, Arrest of labor, Cord prolapsed, Abruption, Maternal hemorrhage

4.0 MANUSCRIPT 2: MODE OF DELIVERY AND SHORT-TERM INFANT HEALTH OUTCOMES IN A PERI-URBAN INDIAN POPULATION

4.1 ABSTRACT

Objective: To determine whether cesarean section delivery is associated with higher reports of adverse short-term infant health outcomes in a peri-urban Indian population.

Methods: Data from a prospective cohort study in Telangana State, India, were analyzed to assess the association between mode of delivery and maternal report of recent infant diarrhea and/or respiratory symptoms at a six month follow-up visit. Inverse probability of treatment weights were applied to log-binomial regression models to account for pre-delivery maternal factors.

Results: Of the 851 singleton infants delivered between 2010 and 2015, 46.7% were delivered by cesarean. Cesarean delivery was not associated with an increased report of infant having one or more of the outcomes (diarrhea, respiratory infection, or difficulty breathing) at six months (adjusted risk ratio (aRR) 0.89, 95% confidence interval 0.76-1.03), nor was it associated with infants having a more severe outcome of both diarrhea and respiratory infection (aRR 1.08, 95% CI 0.58-2.04).

Conclusion: Unlike findings in Western populations, in this peri-urban Indian population, cesarean delivery was not associated with higher reports of short-term adverse gastrointestinal or respiratory infant outcomes. Future research in this cohort could elucidate whether mode of delivery is associated with other adverse outcomes later in childhood.

4.2 INTRODUCTION

Diarrhea and acute respiratory infections are among the leading preventable causes of mortality worldwide in children under age five years old. [112] Risk factors for these conditions include malnutrition, lack of breastfeeding, and environmental exposures related to drinking water, and poor sanitation and hygiene practices. [112] While treatments such as antibiotics and oral rehydration therapy exist, preventing the development of these and other adverse health outcomes is ideal, starting with a healthy immune system.

Neonates are born with an almost sterile gastrointestinal tract which is then colonized by bacteria from their mother and birth environment. [113] As the intestinal microbiome plays an important role in generating host immune defense against pathogens, mode of delivery may influence both short and long term health among infants. [113] According to the hygiene hypothesis, cesarean section delivery increases the risk of immune related conditions in children when they are not exposed to their mother's vaginal and intestinal microbes at birth, but instead to microbes of the mother's skin and the birth environment. [114] [71] This is thought to negatively impact the composition of the infant's intestinal microbiome, impeding the development of a healthy immune system, and possibly leading to later adverse health outcomes.[114] [71]

Observational, population-wide registry research studies have reported associations between cesarean section delivery and health conditions such as asthma, gastroenteritis, and atopic disease. [81,85,86] However, most of these studies have been conducted in high income countries. Less research has been conducted on the impact of mode of delivery on health outcomes in children in low and middle income countries, particularly within the first year of life.

The rate of cesarean delivery in India is high and increasing nationwide, with the most recent cesarean delivery estimate being 17.2% of all births in 2015, up from 8.5% in 2005. [9,100]

Furthermore, an Indian study found that the fecal microflora of neonates at 7 days old differed by mode of delivery. [115] Similar to prior studies, neonates delivered vaginally had bacteria that resembled the mother's vaginal microbiome, whereas those delivered by cesarean had more bacteria associated with the hospital environment. [115] However, the impact of mode of delivery on short-term infant health outcomes in Indian populations is unknown. Determination of adverse outcomes associated with cesarean delivery in this population is important as it would call for programs to reduce the elevated cesarean rates and guide intervention programs among infants born by cesarean.

The purpose of this study is to identify whether infants in a peri-urban Indian population born by cesarean section have higher reports of gastrointestinal (diarrhea), or respiratory (respiratory infection, or difficulty breathing) health problems at six months compared to infants delivered vaginally. In addition, we aim to identify whether other demographic, environmental, or infant feeding factors are associated with adverse health outcomes in this population.

4.3 METHODS

4.3.1 Study population

The LIFE study is a prospective pregnancy cohort study of reproductive aged women residing in a peri-urban area in Telangana State, India, on the outskirts of the city of Hyderabad. Details of the LIFE study design have been previously described. [7] Briefly, the LIFE study was established to assess the effect of the maternal environment on birth outcomes and child development. Between October 2009 and August 2011, 1,227 women were enrolled pre-conception (80%) or in the first trimester of pregnancy (20%). Demographic information was collected at enrollment, details from labor and delivery abstracted from medical records, and follow-up data for mother and child collected by anthropometric assessments and self-report on questionnaires. Follow-up questionnaires are administered with the mother and infant one month postpartum, and at six month intervals until the child is age two years, then annually thereafter.

Between March 2010 and December 2015, 1169 infants were born in the Longitudinal Indian Family Health (LIFE) Study. Infants with complete follow-up data through six months were included in this analysis, resulting in a sample of 851 of infants (73% of births through December 2015). Mothers of infants who did not have six month follow-up in December 2015 were not significantly different from mothers with follow-up in mode of delivery, caste/tribe, or working outside the home (Supporting Information: Table 10). However, more mothers who did not have six month follow-up were of the Hindu religion, reported a lower level of education, were younger at delivery (≤19 years old), and nulliparous compared to mothers with complete follow-up.

4.3.2 Exposure and Outcome variables

The primary exposure was mode of delivery (cesarean section or vaginal delivery) as recorded on the LIFE study labor and delivery abstraction form. Vaginal deliveries included spontaneous vaginal deliveries (n=428), vaginal deliveries with forceps assist (n=23), vaginal deliveries with vacuum assist (n=2), or vaginal deliveries with breech extraction (n=1).

Outcomes were assessed at the six month follow-up visit and include maternal report of infant respiratory infection (cough or cold) in the past month, infant diarrhea in the past month, or infant signs and symptoms of difficulty breathing in the past three months. We assessed two combinations of these outcomes. First, we considered a composite representing one or more of the health outcomes. Second, we categorized an outcome to include both diarrhea and respiratory infection, which we considered to represent more severe morbidity.

4.3.3 Statistical Analysis

Bivariate analyses were conducted to calculate the crude relationship between mode of delivery and infant outcomes using log-binomial regression models. Infant anthropometric assessments, maternal report of infant birth factors, infant feeding, environment, and household hygiene and sanitation practices, were assessed for their association with the outcomes.

4.3.4 Propensity Score Analysis

Propensity score adjustment using inverse probability of treatment weights (IPTW) was used to minimize bias and to balance the exposure groups by pre-delivery factors. A logistic regression model with mode of delivery as the outcome and pre-delivery factors as predictors was used to obtain a probability of delivery by cesarean. These factors encompassed factors pre-pregnancy, prenatal, and during labor and delivery. Common support of the propensity score model was visually evaluated by comparing box plots of the propensity score distribution, and balance of propensity score model was assessed by calculating standardized bias. [116]

4.3.5 Regression Analysis

The inverse of the estimated propensity score was incorporated as a weight in the log-binomial regression models to assess the association between mode of delivery and infant outcomes, obtaining adjusted relative risk (aRR) and 95% confidence intervals. First, the regression models were conducted with the propensity score weight and mode of delivery as the only predictor of the outcomes. Secondary analyses were conducted adjusting for postpartum covariates including infant sex, timing of breastfeeding initiation (<1 hour vs >2 hours), and infant waste disposal method. All analyses were conducted using SAS 9.3 (SAS Institute, Cary, NC).

4.4 RESULTS

4.4.1 Population characteristics

Of the 851 infants with 6 month follow-up in the LIFE study, 46.7% were delivered by cesarean section. Of these, 418 (49.1%) were reported to have had one or more of the outcomes (diarrhea, respiratory infection, or difficulty breathing), and 45 (5.3%) had both diarrhea and respiratory infection in the past month. Differences in characteristics and exposures for infant outcome groups are presented in Table 8. For both outcome groups, there were no significant differences in infant sex, gestational age, birth weight, weight at six months, infant age at the time of questionnaire, although a higher proportion of girls had both diarrhea and respiratory infection compared to boys (p=0.06). Breastfeeding was nearly universal in this population and over 98% of mothers were still breastfeeding at the six month follow-up. Rates of breastfeeding did not differ by infant outcome, although a greater proportion of infants with both diarrhea and respiratory infection had report of later initiation of breastfeeding (≥2 hours after delivery vs ≤1 hour after delivery) (p=0.07). Moreover, more infants with one or more outcomes reported a higher number of supplemental feedings per day.

Environmental factors were not significantly associated with any infant outcome group. Among analyses of hygiene and sanitation factors, a higher proportion of mothers of infants who had one or more outcomes reported disposing of their infants' waste by rinsing the diaper in the toilet/latrine, or in an open ditch, or leaving it in the open, while a smaller proportion buried the waste or disposed into the garbage. A higher proportion of mothers of infants who had both diarrhea and respiratory infection reported disposing of their infants' waste by rinsing the diaper in the toilet/latrine, or in an open ditch, while a smaller proportion buried or left it in the open.

For maternal report of health conditions, three mothers reported having diarrhea in the past month, and twelve reported having respiratory infection in the past month. A higher proportion of infants in both outcome groups had mothers with these ailments, although temporality of infection (mother infected first or infant infected first) could not be established.

4.4.2 Propensity Score Analysis

The box plots evaluating common support of the propensity score distributions had overlapping confidence intervals for vaginal and cesarean delivery, showing that observations from both exposure groups are available across the range of propensity scores. The unstandardized bias of pre-delivery maternal characteristics included in the propensity score model to predict mode of delivery show that before applying the IPTW, three of the variables exceeded the threshold of a difference of 0.25 (absolute value) (Supporting Information: Table 11). After applying the IPTW, the standardized bias for all except two of the variables were below the more conservative threshold of 0.10 (absolute value). This demonstrates good balance in the weighted distributions between exposure groups.

4.4.3 Regression Analysis

In the unadjusted log-binomial regression model predicting one or more of the outcomes, cesarean delivery was associated with a 12% reduced risk of the infant having one or more of the outcomes, although the relationship was of borderline statistical significance (RR 0.88, 95% CI 0.77-1.01, Table 9). In the model adjusting for the IPTW, the relative risk was not attenuated (aRR 0.89, 95% CI 0.76-1.03). In secondary analysis adjusting for the IPTW and infant sex, hours after birth that breastfeeding was initiated, and infant waste disposal method as covariates, the association did not change (aRR 0.88, 95% CI 0.76-1.03) (Supporting Information: Table 12).

Similarly, the log-binomial models of mode of delivery predicting concomitant diarrhea and respiratory infection were not statistically significant in unadjusted (RR 0.91, 95% CI 0.52-1.62), or IPTW adjusted analysis (aRR 1.08, 95% CI 0.58-2.04). Additional adjustment for infant sex, hours after birth that breastfeeding was initiated, and infant waste disposal method in secondary analysis further nullified this relationship (aRR 0.94, 95% CI 0.48-1.85) (Supporting Information: Table 12).

4.5 DISCUSSION

Infants in the LIFE study delivered by cesarean do not have a higher risk of adverse gastrointestinal or respiratory health outcomes at six month follow-up compared to those delivered vaginally. IPTW adjusted analyses were not statistically significant, but suggested a decreased risk of one or more outcomes in infants delivered by cesarean compared to vaginal delivery, but a modestly increased likelihood of report for comorbid respiratory infection and diarrhea, which was nullified when other postpartum covariates were added to the model.

Our study focused on assessing short-term infant health and did not find a significant association between mode of delivery and respiratory or gastrointestinal health problems after accounting for pre-delivery factors in our analysis. Studies in similar demographic populations in Malaysia, Iraq, and Brazil have focused on the association of cesarean delivery on asthma in children ranging in age from six to 15 years, and have also found no association. Rather, other factors such as family history of allergic disease, parental education, crowding in the home, and exposure to cigarette smoke were found to be predictive of the adverse health outcomes. [117] [118] [119] Similar to our results, these findings suggest that children in low and middle income countries have a range of exposures that can lead to adverse respiratory health outcomes other than mode of delivery.

Conversely, a longitudinal study in India and Vietnam found that the likelihood for care-giver reported asthma at age 8 years was twice as high for those delivered by cesarean compared to vaginally delivered, after accounting for socio-demographic risk factors in multivariable analysis. [83] This finding was similar to studies in western countries, which have found an increased association between mode of delivery and adverse infant health outcomes. Using a Swedish population-based registry to assess the association between mode of delivery with asthma and gastroenteritis, one study found that hospital admission for asthma or gastroenteritis in children at least a year old was increased in those delivered by cesarean. [81] The link between cesarean delivery and gastrointestinal symptoms in the first year of life was also found in a German cohort, and in infants born preterm in an Australian population based study. [80] [79]

One factor that has been shown to play a role in previous studies is the rate of breastfeeding, which has been found to be decreased in pre-labor cesarean deliveries. [120] In populations with universal breastfeeding through six months, such as ours, the effect of mode of delivery on infant health may be negligible, as breast milk also has immune building properties. [79] A study of the microbes in breast milk samples of Canadian women found that breastmilk contained the beneficial *Lactobacillus* bacteria regardless of mode of delivery.[121] Thus, in our population with high breast feeding rates, even infants delivered by cesarean could receive beneficial microbes to promote development of a healthy immune system via breast feeding.

One of the major strengths of our study is that we were able to control for the effect of pre-delivery maternal factors that may have biased a woman towards cesarean delivery. In addition, as this is a prospective study we are able to assess short-term infant health outcomes, which offers a unique perspective in the literature that is dominated by the assessment of mode of delivery in older children in western countries. Further, as this is a population-based study, the findings are generalizable to the surrounding population in this peri-urban setting in Telangana state. Lastly, we had the benefit of having a large sample size of over 800 infants.

We were limited in our statistical power to detect differences by health outcomes independently, but compensated for this by creating composite variables by grouping the adverse respiratory and gastrointestinal outcomes. This allowed us to assess combinations of both common and more severe outcomes. Unlike our exposure which is verified on medical records, the outcomes were determined by maternal report and not clinically confirmed. Thus, outcome misclassification is possible. While our study was limited to the assessment of short- term infant outcomes, future studies in our population can consider both short-term infant and longer term childhood outcomes, including asthma. There is likely unmeasured confounding for predictors that we could not assess, including parental and family history of asthma or atopic disease. In addition, differences in maternal characteristics by religion, education, age, and parity in mothers with and without follow-up through six months may have affected our results. These differences may reflect the cultural practices of a woman relocating from her marital home to her mother's residence when delivering a first child. [7] Lastly, onset of labor was not measured in our study; therefore, some infants delivered by cesarean may have been exposed to their mother's vaginal microbiota during a period of labor, which would negate the 'hygiene hypothesis'. Additional studies in low and middle income settings are needed to assess the causal associations between mode of delivery, respiratory infection, and diarrhea, accounting for timing of labor.

Our study shows that mode of delivery may not significantly impact infant health outcomes in peri-urban settings in India, and possibly other low and middle income countries. While research in urban, western countries has found an association between mode of delivery and adverse infant outcomes, our study suggests that other factors include infant sex, mother's health, and sanitation/hygiene perhaps play a more significant role in infant respiratory and gastrointestinal health in peri-urban settings.

4.6 TABLES

Table 8 Characteristics Associated with Report of Infant Diarrhea, Respiratory Infection, or Difficulty Breathing at 6 months of age in the LIFE study

		Diarrhea or Respiratory Infection and/or Difficulty Breathing			Diarrhea and Respiratory Infection		
	Category	Yes % N=418	No % N=433	p-value	Yes % N=45	No % N=806	p-value
Infant Characteristics							
Infant sex	Boy	53.5	51.1	0.47	38.6	53	0.06
	Girl	46.5	48.9		61.4	47	
Gestational age at birth	Mean weeks ± SD	38.85 ± 2.41	38.84 ± 2.45	0.93	38.86 ± 2.43	38.60 ± 2.53	0.48
Birth weight	Mean kg ± SD	2.80 ± 0.44	2.82 ± 0.45	0.46	2.82 ± 0.44	2.73 ± 0.47	0.21
Weight at 6 months	Mean kg ± SD	7.12 ± 1.01	7.11 ± 1.07	0.95	7.13 ± 1.04	6.85 ± 1.01	0.09
Age at time of questionnaire	Mean months ± SD	6.50 ± 0.97	6.49 ± 0.75	0.90	6.49 ± 0.87	6.56 ± 0.81	0.63
Infant Feeding and Immunization							
Ever breastfed	Yes	100	99.5	0.17	100	99.8	0.74
Time to breast feeding initiation from birth (hours)	≤1 hour	70.3	69.6	0.81	57.8	70.6	0.07
	2-20 hours	29.7	30.4		42.2	29.4	
Breastfeeding at 6 months	Yes	98.1	97.7	0.68	100	97.7	0.31
Given anything other than breast milk to infant	Yes	87.8	90.3	0.25	82.2	89.4	0.13
Food given	Water	4.9	4.6	0.93	5.6	4.7	0.82
	Cow's or powdered milk	1.4	1.0		2.8	1.1	
	Rice/dal	18.9	17.7		19.4	18.2	
	Other	74.8	76.6		72.2	75.9	
Infant given water to drink	Yes	86	89.8	0.09	86.4	88	0.74
Number of times a day infant fed something other than breast milk	Mean ± SD	3.7 ± 2.4	3.3 ± 2.1	0.04	3.53 ± 2.31	2.81 ± 1.75	0.02
Infant received vaccinations (BCG, Measles, Polio, DPT, Hepatitis B)	Yes	100	100	-	100	100	-

Table 8 – Continued

Environmental							
Number of people in the household	3-5 people	51.4	49.3	0.70	55.6	50.1	0.76
	6-12 people	46.9	48.4		42.2	48.0	
	13+ people	1.7	2.3		2.2	2.0	
Water source for drinking	Purchased cans	82.4	81.9	0.43	84.1	82	0.84
	Piped (tap)	17.4	17.2		15.9	17.3	
	Other	0.2	0.9		0	0.6	
Type of fuel used in the household	Firewood/ crop residuals	14.7	14.1	0.96	13.6	14.4	0.81
	Electricity	0.5	0.7		0	0.6	
	LPG/Natural gas	83.9	83.8		84.1	83.8	
	Kerosene	0.7	0.9		2.3	0.8	
	Other	0.2	0.5		0	0.4	
Someone in household smokes	Yes	15.9	14.1	0.46	8.9	15.3	0.24
Family keeps animals inside or near home	Yes	17.8	19.3	0.59	18.2	18.6	0.94
Used pesticides in past month	Yes	0	0.2	0.33	0	0.1	0.81
Hygiene/ Sanitation							
Infant wears diaper in the house at 6 months	Yes	47.2	44.8	0.48	45.5	46	0.94
Infant wears diaper outside the house at 6 months	Yes	81.9	83.6	0.51	84.1	82.7	0.81
Where is your infants waste disposed?	Put/rinsed into toilet or latrine	23.5	20.3	0.016	37.8	21	0.004
	Put/ rinsed into open drain or ditch	31.6	25.6		37.8	28	
	Buried	19.9	29		4.4	25.7	
	Thrown into garbage	10.4	12.4		11.1	11.5	
	Left in the open	14.6	12.7		8.9	13.9	
Maternal Health at 6 months							
Ailments in the past month	Maternal Diarrhea	0.7	0	0.08	2.3	0.2	0.03
	Maternal Respiratory Infection	2.4	0.5	0.02	11.4	0.9	<0.0001

Table 9 The association between mode of delivery and infant health outcomes at 6 months in the LIFE study, adjusting for pre-delivery maternal factors using propensity score analysis

	≥1 outcome at 6 months (Diarrhea, difficulty breathing, or respiratory infection)		Both diarrhea and respiratory infection at 6 months	
	Unadjusted RR	Adjusted RR	Unadjusted RR	Adjusted RR
Cesarean vs Vaginal delivery	0.88 (0.77-1.01)	0.89 (0.76-1.03)	0.91 (0.52-1.62)	1.08 (0.58-2.04)

*Variables in propensity score model: BMI, parity, education; first trimester prenatal vitamin use, diagnosis of feet swelling during third trimester, unable to perform regular duties due to illness/injury during third trimester, prenatal vaginal bleeding; age at delivery, and any labor and delivery complications

Table 10 Comparison of characteristics of mothers who had completed the 6-month follow-up in December 2015 to those who had not completed 6 month follow-up

	Births with follow-up N=851 %	Births without follow-up N=286 %	p-value
Mode of delivery			0.27
Vaginal Delivery	53.2	57.0	
Cesarean delivery	46.8	43.0	
Religion			
Hindu	88.1	92.7	0.04
Muslim	7.6	5.9	
Christian	4.2	1.4	
Caste			0.14
Scheduled caste	20.6	21.3	
Scheduled tribe	7.3	11.5	
Backward caste	56.9	53.2	
None of the above	15.3	14.0	
Level of education			0.03
None	13.4	19.2	
Primary/Middle School	25.4	27.3	
Secondary School	51.5	47.2	
Higher education	9.8	6.3	
Age at delivery (years)			<0.0001
≤19	8.1	15.4	
20-24	63.5	66.4	
25+	28.4	18.2	
Parity			0.02
Multiparous	79.7	72.7	
Nulliparous	20.3	27.3	
Works outside the home	9.1	8.0	0.59

*Comparison limited to 1,137 births delivered at least six months prior to December 2015

Table 11 Maternal pre-delivery characteristics by mode of delivery and standardized bias before and after weighting

Characteristic	Vaginal Delivery n=454	Cesarean Delivery n=397	Unweighted Standardized Bias†	Weighted Standardized Bias†
	n(%)	n(%)		
Pre-pregnancy				
BMI (Mean kg/m^2 (Std. Dev))	19.5 (2.9)	20.6 (3.6)	0.34	-0.04
Multiparous	349 (81)	286 (78)	-0.09	-0.03
Level of education				
None	68 (15)	46 (12)	0.23	0.09
Primary	126 (28)	88 (22)		
Secondary	227 (50)	213 (54)		
Higher education	33 (7)	50 (13)		
Prenatal				
First trimester prenatal vitamin use	111(26)	152(42)	0.33	-0.05
Diagnosed with feet swelling during third trimester	25(5.7)	37(9.7)	0.15	-0.12
Not able to do regular duties due to illness/injury during third trimester	8(1.8)	17(4.5)	0.15	0.05
Prenatal vaginal bleeding	5(1.2)	14(3.8)	0.17	-0.17
Delivery				
Age at delivery	22.9 (2.9)	23.5 (3.1)	0.20	-0.05
Any labor and delivery complications	42(9.3)	142(36)	0.67	-0.05

† Standardized bias = difference in means or proportions divided by standard error; imbalance defined as an absolute value >0.25

Table 12 The association between mode of delivery and infant health outcomes at 6 months in the LIFE study, adjusting for pre-delivery maternal factors using propensity score analysis and postpartum covariates

	≥1 outcome at 6 months (Diarrhea, difficulty breathing, or respiratory infection)		Both diarrhea and respiratory infection at 6 months	
	Unadjusted RR	Adjusted RR	Unadjusted RR	Adjusted RR
Cesarean vs Vaginal delivery	0.88 (0.77-1.01)	0.88 (0.76-1.03)	0.91 (0.52-1.62)	0.94 (0.48-1.85)
Infant sex: girl vs boy	0.95 (0.83-1.09)	0.91 (0.78-1.06)	1.74 (0.96-3.14)	1.71 (0.84-3.48)
Infant breastfed 2+ hours after birth vs <1 hour	0.99 (0.85-1.15)	0.87 (0.74-1.03)	1.87 (1.03-3.37)	1.55 (0.79-3.03)
Diaper/Waste disposal method				
Put/rinsed into toilet or latrine	1.17 (0.90- 1.52)	1.17 (0.88-1.56)	1.76 (0.67-4.64)	1.57 (0.48-5.18)
Put/ rinsed into open drain or ditch	1.20 (0.94- 1.55)	1.19 (0.90- 1.56)	1.35 (0.51-3.57)	1.39 (0.43-4.49)
Buried	0.88 (0.67- 1.16)	0.78 (0.57- 1.06)	0.18 (0.04-0.93)	0.09 (0.008-1.15)
Thrown into garbage	Ref.	Ref.	Ref.	Ref.
Left in the open	1.16 (0.88- 1.55)	1.12 (0.81- 1.54)	0.67 (0.18-2.42)	0.67 (0.14-3.09)

*Variables in propensity score model: BMI, Parity, Level of education; First trimester prenatal vitamin use, Diagnosed with feet swelling during third trimester, Not able to do regular duties due to illness/injury during third trimester, Prenatal vaginal bleeding; Age at delivery, Any labor and delivery complications

5.0 MANUSCRIPT 3: ADVERSE INFANT OUTCOMES ASSOCIATED WITH CESAREAN SECTION DELIVERY IN INDIA: A RETROSPECTIVE ANALYSIS OF NATIONAL SURVEY DATA

5.1 ABSTRACT

Objective: To assess the impact of cesarean section delivery on adverse infant health outcomes and neonatal mortality in India after accounting for maternal, socioeconomic, and healthcare factors.

Methods: Cross-sectional data was obtained from responses of women aged 15 to 49 surveyed in the 2005-2006 India National Family Health Survey who reported their most recent singleton birth was in the previous five years. Inverse probability of treatment weighted logistic regression analysis was used to obtain adjusted odds ratios and 95% confidence intervals, adjusting for the association between mode of delivery and maternal, socioeconomic, and antenatal care factors. Weights were obtained from propensity score modeling of mode of delivery predicted by factors including place of residence, wealth index, education, receipt of antenatal care, and delivery at private or public hospital. Outcomes included maternal report of diarrhea and acute respiratory infection (ARI) in the previous two weeks in infants age six months or less, and neonatal death (within the first month of life) .

Results: Of the 36,501 reported singleton births, 4,392 (12.0%) were delivered by cesarean, 222 (4%) of the infants aged six months or less had report of recent diarrhea and ARI, and 753 (2.1%) neonatal deaths were reported. After applying the inverse of the propensity score as weights to the logistic regression model, cesarean delivery was not associated with infant diarrhea and ARI (aOR 0.91, 95% CI 0.61-1.36), but was associated with neonatal death (aOR 1.32, 95% CI 1.04-1.67).

Conclusions: Using nationally representative data for India, cesarean section delivery was found to be associated with neonatal death after accounting for maternal, socio-economic, and healthcare factors associated with mode of delivery. Further exploration of the relationship between cesarean delivery and adverse infant outcomes is needed accounting for factors that may have indicated cesarean delivery.

5.2 INTRODUCTION

Cesarean section delivery has been found to be associated with adverse infant outcomes, including impaired gastrointestinal and respiratory health, and mortality.[81] [70] In many countries, place of residence (urban or rural) can determine the quality of maternal care that is available and accessed, and can also affect infant outcomes. Furthermore, numerous other factors are associated with mode of delivery, including receipt of antenatal care, maternal characteristics, and societal norms.[122]

Cesarean delivery rates have been rapidly increasing worldwide.[8] Currently, it is estimated that almost one in five births globally are delivered by cesarean.[8] An analysis of national data from 159 countries found that neonatal and maternal mortality rates were lowest among countries with national cesarean delivery rates between 5% and 10%, but were higher and stable among countries with cesarean delivery rates greater than 10%.[123] This implies that there are no additional benefits of high cesarean delivery rates in addressing mortality. Moreover, the World Health Organization recommends that the cesarean delivery rate should not exceed 15% of births in all regions.[8]

Cesarean delivery rates are also increasing nationally in India. The 2015-2016 India National Family Health Survey (NFHS-4) estimates that 17% of all births nationwide are delivered by cesarean.[9] However, it is unknown how socioeconomic, healthcare, and maternal factors collectively contribute to the cesarean delivery rate in India, which in turn could impact infant outcomes. The purpose of this study is twofold, 1) to identify key socioeconomic, health care, and maternal factors associated with cesarean delivery in India, and 2) to determine whether cesarean delivery is associated with adverse infant outcomes in a nationally representative survey.

5.3 METHODS

5.3.1 Study population and Sampling

We obtained data from the 2005-2006 India National Family Health Survey (NFHS-3), a nationally-representative cross-sectional household survey conducted by the International Institute for Population Sciences (IIPS) and the Demographic and Health Survey (DHS) program.[100] The main purpose of the NFHS is to provide reproductive, maternal and child health information for India.[98] Four cycles have been conducted; in 1992-1993, 1998-1999, 2005-2006, and 2015-2016. Data was requested from and provided via the DHS program, with the most recent available data being from the 2005-2006 cycle.

The survey sample for NFHS-3 was obtained by two-stage sampling in rural areas and three-stage sampling in urban areas, in each of the 29 Indian states. [100] Questionnaires were implemented in two phases: from November 2005 to May 2006 or April 2006 to August 2006. Ever-married women ages 15 to 49 years were interviewed with the "Woman's Questionnaire" regarding their children and pregnancies.

Singleton births in the previous five years were included in our analysis. Information on antenatal care and prenatal health was only collected for the most recent birth. In total, 124,385 women age 15-49 years were surveyed in the NFHS-3. After excluding multiple births, and women whose most recent births were not in the prior 5 years, the final sample included responses from 36,501 women.

5.3.2 Key Measures

Mode of delivery was determined by self-report to the question “Was (Child’s Name) delivered by caesarean section?”

We assessed two infant outcomes. First, recent adverse health was determined by maternal report of whether the infant had diarrhea and symptoms of acute respiratory illness (ARI; cough accompanied by short, rapid breathing) in the two weeks before the interview in infants aged six months or less (n=5,433). Second, neonatal death was determined by maternal report of the child’s age at death. Of the 1,238 reported child deaths, 753 were in the first month of life.

5.3.3 Predictor variables

The predictor variables for cesarean delivery and infant outcomes assessing demographics, antenatal care (ANC), and prenatal health conditions were determined by maternal self-report. Demographic variables included place of residence (urban or rural), type of city, religion, head of household caste, wealth index (a DHS created composite variable measuring household wealth), maternal age, education, marital status, whether she was working, and partner’s occupation. ANC variables included number of ANC visits, whether ANC was received at a government facility or private hospital, and whether delivery occurred in public or private sector facility. Reproductive history variables included parity, and whether she had ever terminated a pregnancy. Body mass index was determined using the WHO recommended cut-offs for public health action in Asian populations (underweight ≤18.49, normal 18.5-22, overweight/obese ≥23). [105] Few prenatal health conditions are assessed in the survey. Available variables included maternal iron supplementation, day or night vision difficulties, use of intestinal parasitic medication, convulsions during pregnancy, body swelling, excessive fatigue, or vaginal bleeding.

Infant covariates included infant sex, year of birth, and maternal report of size at birth. Breastfeeding status in living infants assessed if they were ever breastfed, timing of breastfeeding initiation, and whether the infant was currently breastfeeding. Infant's gestational age at birth was not assessed in the NFHS-3.

5.3.4 Statistical Analysis

5.3.4.1 Factors associated with Cesarean Section Delivery

Proportions of socioeconomic and maternal factors were obtained with univariate analysis using national-level sampling weights to account for the differential non-response rates of interviews. Associations between mode of delivery and categorical variables were determined by the Wald's chi-square test.

Place of residence (urban or rural) was the main predictor for mode of delivery. Secondary predictors that increase the likelihood for cesarean delivery were selected for the multivariable model predicting mode of delivery by whether they changed the risk estimate of place of residence by >10% in bivariate logistic regression models. A final multivariable logistic regression model with place of residence and the selected secondary predictors was used to determine independent associations with mode of delivery, obtaining adjusted odds ratios and 95% confidence intervals.

5.3.4.2 The Effect of Cesarean Section Delivery on Adverse Infant Outcomes

The multivariable logistic regression model predicting cesarean delivery was used to create propensity scores for mode of delivery. The propensity scores aim to balance the baseline factors associated with mode of delivery by each exposure group (cesarean vs vaginal delivery), mimicking randomization of baseline factors and reducing bias for known confounders in the relationship between mode of delivery and infant outcomes.

The crude relationship between mode of delivery and infant outcome was assessed by logistic regression, obtaining odds ratios and 95% confidence intervals. The inverse of the propensity score was applied as a weight to the logistic regression models to obtain adjusted odds ratios for the relationship between mode of delivery and the infants having the adverse health outcomes diarrhea and ARI, and with neonatal death.

Secondary analysis was conducted in infants whose mothers recalled or had a health card indicating the infant's birthweight as >2500g in order to assess the association between neonatal mortality and mode of delivery in normal weight babies only.

All analyses were conducted using SAS 9.3 (SAS Institute, Cary, NC) and STATA 12 (StataCorp, College Station, TX).

5.4 RESULTS

Of the 36,501 singleton births reported in the previous 5 years, 4,392 (12%) were delivered by cesarean. Of the children who were still alive, 5,433 were age six months and under, and 222 (4%) of those had reports of the severe outcome of both acute respiratory illness and diarrhea in the previous two weeks.

5.4.1 Factors associated with Cesarean Section Delivery

Table 13 presents the overall characteristics of women included in the 2005-2006 DHS with a birth in the previous 5 years, applying survey weights to obtain nationally representative proportions. The demographic variables head of household caste, wealth index, and maternal education level were included in the final multivariable model predicting mode of delivery, based on changing the estimate of place of residence by >10% in bivariate analysis. In addition, number of ANC visits (≤5 or >5), timing of first ANC visit, place where ANC was received (government or private facility), place of delivery (public or private sector), parity, and whether the woman supplemented iron during her pregnancy were included in the final multivariable model.

Table 14 presents the crude and adjusted associations of these predictors and mode of delivery. After adjusting for the secondary predictors, place of residence was not associated with mode of delivery (adjusted odds ratio (aOR) 1.01, 95% CI 0.93-1.10). Being in the richer or richest wealth index quintiles compared to the poorest was positively associated with cesarean delivery (aOR 1.51, 95% CI 1.16-1.96, and aOR 1.65, 95% CI 1.26-2.16, respectively). In addition, higher education compared to no education (aOR 1.48, 95% CI 1.26-174), attending ≥5 ANC visits (aOR 1.45, 95% CI 1.32-1.60), receiving ANC at a private hospital (aOR 1.17, 95% CI 1.05-1.30), and delivery at a private hospital (1.48, 95% CI 1.34-1.64) were positively associated with cesarean delivery.

5.4.2 The Effect of Cesarean Section Delivery on Adverse Infant Outcomes

Table 15 presents the characteristics of infant's age six months or less who were reported to have the adverse health outcome of both diarrhea and ARI in the two weeks prior to the interview, and those who did not. A higher proportion of those who had both diarrhea and ARI were male, and a higher proportion were born in 2005 compared to infants who did not have report of the adverse outcomes.

Table 16 presents the crude and adjusted odds ratios for the association between mode of delivery and whether the infant had concomitant diarrhea and ARI in the previous two weeks. In both the crude and adjusted models, cesarean delivery was not statistically significantly associated with both outcomes, (OR 0.79, 95% CI 0.50-1.25 and aOR 0.91, 95% CI 0.61-1.36, respectively). The estimates for mode of delivery were also not significant in models predicting diarrhea and ARI individually (Table 17).

Table 18 presents the characteristics of infants that died in the first month of life compared to those who were still alive. A greater proportion of infants who died were born in 2005 or 2006. A smaller proportion of those who died were reported to have ever been breastfed.

Table 19 presents the crude and adjusted odds ratios between neonatal mortality and mode of delivery. In the unadjusted model, cesarean delivery was not significantly associated with neonatal mortality (OR 0.81, 95% CI 0.63-1.03). After adjusting for the inverse of the propensity score as a weight in the logistic regression model, cesarean delivery was positively associated with neonatal mortality (aOR 1.32, 95% 1.04-1.67).

Of all 36,501 deliveries, 16,204 (44%) reported a birthweight, and 13,110 of these had a reported weight of >2500g, 98 of which were neonatal deaths. In secondary analyses, the unadjusted relationship between neonatal mortality and cesarean delivery in infants who weighed >2500g at birth was not statistically significant (OR 1.30, 95% CI 0.84-2.01). After applying the inverse of the propensity score to the model there was a positive association (aOR 1.58, 95% CI 1.03-2.42).

5.5 DISCUSSION

In our analysis of nationally representative data for India in 2005-2006, we found that socioeconomic and healthcare factors are associated with cesarean delivery. Specifically, being wealthy, having a high level of education, having more than five ANC visits, and receiving care at a private hospital for ANC and delivery were predictive of cesarean delivery. After controlling for these factors using propensity score analysis, we found that cesarean delivery was not associated with maternal report of concomitant diarrhea and ARI among infants age six months, but a positive association with neonatal death was found.

Our study found that place of residence is associated with a three-fold increased likelihood of cesarean delivery in crude analysis. However, in a multivariable model with other socioeconomic, health care, and maternal health factors, the association between place of residence and mode of delivery was nullified. Previous research studies using DHS data have found that place of residence is a major predictor of mode of delivery. A descriptive study of trends of cesarean delivery using national data found that in a sample of 82 low and middle income countries, rates of cesarean delivery in urban areas were on average three times higher than in rural areas between 1990 and 2003. [124] Another analysis of the 1992-1993 NFHS data specifically in the southern Indian state of Kerala found that the proportion of cesarean deliveries was higher in urban areas, which the authors attributed to the extent of health service utilization in urban areas of India. [30] On the other hand, an analysis of 20 years of national data found that the high cesarean delivery rate in China is partly attributable to residence in urban or rural areas rather than household wealth, suggesting that regional socioeconomic factors had greater impact than individual factors such as income, education, or health insurance. [125] With our analysis including place of residence as the main predictor of mode of delivery in the multivariable model, identified other important predictors, some of which are potentially modifiable.

Our finding that wealthier women are more likely to undergo cesarean delivery than poorer women is consistent with prior studies. Using a series of cross-sectional surveys, a study assessing national-level trends of cesarean delivery rates in 26 countries found that South Asian women in the highest wealth quintile received more cesareans compared to those in the poorest quintiles. [126] Similarly, an analysis of national data in Jordan found that mothers in poor wealth categories had lower rates of cesarean delivery compared to wealthier mothers. [127] Material wealth may indicate having the resources to afford access to more costly medicalized treatment. This is related to receiving care in private vs public health care facilities, which was also associated with an increased likelihood of cesarean delivery in our study and in other studies in South Asia. [62]

Our study found no association between cesarean delivery and maternal report of recent (past two weeks) concomitant diarrhea and acute respiratory infection among infants aged six months or less, even after adjusting for confounding socioeconomic and healthcare variables. This is consistent with findings from some studies conducted in low and middle income countries, which have found that other factors such as family health history and the child's environment affect adverse health outcomes.[118] [119] In contrast, studies in western countries tend to find an increased risk of adverse health outcomes in children delivered by cesarean. [81] [86] This relates to the theory that infants delivered by cesarean are exposed to different bacteria at birth compared to infants delivered vaginally and thus may have a propensity towards immune related conditions throughout their lives. [71] Our findings suggest that in India, on a population level, mode of delivery is not the most important predictor for the outcomes of recent gastrointestinal and respiratory adverse health in infants.

With 753 neonatal deaths, the neonatal mortality rate in our study sample of most recent births between 2001 and 2006 was 21 neonatal deaths per 1000 live births, which is similar to the 2015 global rate of 19 neonatal deaths per 1000 live births, but lower than the national 2015 estimate for India of 28 neonatal deaths per 1000 live births. [69] Our study found an association with cesarean delivery and neonatal mortality, after adjusting for socioeconomic, and healthcare confounders using inverse probability of treatment weighting. Our finding is consistent with a previous research study of nationally representative demographic and health survey (DHS) data from 46 countries with cesarean delivery rates ranging between 0% and 15%, in which neonatal mortality was greatest among countries with the low and medium rates of cesarean. [70] Another study of data from 126 countries found that cesarean delivery was positively associated with maternal, infant and neonatal mortality in countries with cesarean delivery rates over 15%. [3] Similar to our study, they accounted for socioeconomic variables in their analyses, which indicates the important role of macro-level factors on cesarean delivery, and possibly access and use of healthcare in general, and neonatal mortality. However, not all multinational studies have found a positive association between cesarean delivery and neonatal mortality. Two studies that each included data from over 100 countries found an inverse association between cesarean rates and neonatal mortality rates. [128,129] These conflicting findings point to the complexity in studying associations at the population level, and further investigation into the maternal health factors associated with neonatal mortality is needed.

Strengths of our study include using a large, nationally representative dataset, which provided enough statistical power to assess rare outcomes. To determine the adjusted impact of cesarean delivery on infant outcomes, we used propensity score analysis to balance exposure groups, which has not previously been done with Indian national data. Furthermore, some previous studies examining the relationship between mode of delivery and adverse infant outcomes did not control for socioeconomic factors. Thus, their findings were likely confounded as socioeconomic status can affect both mode of delivery and infant outcomes, as shown in our study.

A limitation of our study is that we only had access to data for the 2005-2006 NFHS. Thus, our study was unable to examine the most contemporary data. As cesarean delivery has increased in India over the past decade, the impact of cesarean delivery may be underestimated in our study. We were also unable to determine indication for cesarean delivery, which was also obtained by self-report. In addition, we did not have a measure for gestational age at birth, which is an important predictor of adverse infant outcomes. However, we were able to analyze a subset of infants with recorded or recalled birthweight and exclude infants weighing <2500g, as a proxy for excluding infants who were likely born preterm or with medical conditions, and the positive association between cesarean delivery and neonatal death remained after adjusting for confounders. We acknowledge that there may still be residual confounding by variables not measured in the survey. Lastly, all of our key measures were determined by self-report, which could lead to over or under-reporting, and bias our estimates. However, the interview process is standardized with trained interviewers to decrease respondent bias, and studies have shown that retrospective maternal report in the DHS are reliable, including report of cesarean delivery. [130]

With the increasing cesarean delivery rate in India, there is a need to consider interventions to prevent adverse outcomes, particularly mortality. It is important to identify whether high cesarean delivery rates in India are due to misuse of medical technology and not medical indication, since overuse of this important obstetric decision can have negative consequences.

5.6 TABLES

Table 13 Characteristics of Women with Singleton Deliveries in the 2005-2006 India National Family Health Survey

	Vaginal Delivery N=32,109 %	**Cesarean Delivery** N=4,392 %	**P-value***
Demographics			
Place of residence type			
Urban	24.1	51.5	<0.0001
Rural	75.9	48.5	
City/Town/Countryside			
Mega city	2.2	4.9	<0.0001
Large city	5.5	14.3	
Small city	6.5	14.3	
Large town	1.8	3.0	
Small town	8.0	15.0	
Rural	75.9	48.5	
Religion [c]			
Hindu	78.8	80.0	<0.0001
Muslim	16.8	12.3	
Christian	1.9	3.9	
Sikh	1.1	2.5	
Buddhist	0.7	0.4	
Other	0.7	0.9	
Head of Household Caste			
Scheduled Caste	21.5	14.2	<0.0001
Scheduled tribe	10.4	3.1	
Other backward caste	42.2	38.6	
None of them	26.0	44.1	
Wealth Index			
Poorest	26.3	4.1	<0.0001
Poorer	23.1	8.6	
Middle	20.0	15.2	
Richer	17.5	25.6	
Richest	13.0	46.6	
Age group			<0.0001
15-19	7.7	5.7	
20-24	33.9	30.6	
25-29	32.2	36.2	
30-34	16.5	19.5	
35-39	6.9	6.4	
40+	2.8	1.6	
Maternal highest education level			<.0001
No education	51.0	13.7	
Primary	14.5	9.9	
Secondary	30.3	54.4	
Higher	4.2	22.0	
Current marital status			0.4649
Married	98.3	98.5	
Not married	1.7	1.5	
Respondent currently working			<.0001
No	69.0	78.7	
Yes	31.0	21.3	

Table 13 - Continued

Partners occupation			<.0001
did not work	1.0	1.3	
professional/technical/managerial	5.3	13.3	
clerical	2.9	7.0	
sales	12.5	21.5	
agricultural	31.9	16.0	
services	4.7	6.4	
skilled and unskilled manual	41.7	34.6	
Antenatal Care			
No ANC received	25.2	1.9	<.0001
Number of ANC visits			<.0001
<5	74.5	28.5	
≥5	25.5	71.5	
ANC received at government/municipal hospital	19.8	21.4	0.0725
ANC received at private hospital/maternity	36.1	67.4	<.0001
Place of delivery			
Public sector [a]	50.9	31.9	<.0001
Private sector [b]	49.1	68.1	
Reproductive history			
Parity			
1 child	24.2	48.8	<.0001
2 children	27.8	37.0	
3+ children	47.9	14.3	
Ever had a terminated pregnancy	18.3	20.5	0.0126
Anthropometrics			
BMI Category (WHO South Asian cut-offs)			<.0001
<18.49 kg/m^2	42.2	22.7	
18.5-22 kg/m^2	44.5	36.0	
≥23 kg/m^2	13.3	41.3	
Prenatal Health			
Prenatal iron supplementation	63.1	86.7	<.0001
Difficulty with daylight vision during pregnancy	6.5	4.7	0.0002
Difficulty with night blindness during pregnancy	9.4	2.8	<.0001
Took drugs for intestinal parasites	3.6	5.9	<.0001
Convulsions during pregnancy not from fever	10.6	6.4	<.0001
Swelling of legs, body, or face	24.3	31.6	<.0001

Table 13 - Continued

Excessive fatigue	47.8	46.9	0.3907
Vaginal bleeding	4.1	6.7	<.0001

*Determined by Wald's X^2 after applying national survey weights

[a] Government/municipal hospital, government dispensary, UHC/UHP/UFWC, CHC/Rural hospital/PHC, Sub-centre, Other public

[b] Private hospital/maternity, Other Private

[c] Other Religions: Jain, No religion, Donyi polo, Other

Table 14 Associations between mode of delivery and maternal and socioeconomic factors in the 2005-2006 India National Family Health Survey

	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
Demographics		
Place of residence type		
Urban	3.13 (2.93-3.35)	1.01 (0.93-1.10)
Rural	Ref.	Ref.
Head of Household Caste		
Scheduled Caste	Ref.	Ref.
Scheduled tribe	0.49 (0.42-0.57)	**0.70 (0.59-0.84)**
Other backward caste	1.32 (1.19-1.46)	0.95 (0.84-1.07)
None of them	2.27 (2.05-2.50)	1.0 (0.89-1.12)
Wealth Index		
Poorest	Ref.	Ref.
Poorer	2.44 (1.92-3.10)	1.26 (0.95-1.67)
Middle	4.81 (3.87-6.0)	1.28 (0.98-1.66)
Richer	10.23 (8.29-12.62)	**1.51 (1.16-1.96)**
Richest	23.82 (19.39-29.28)	**1.65 (1.26-2.16)**
Highest education level		
No education	Ref.	Ref.
Primary	2.29 (1.99-2.62)	1.04 (0.88-1.22)
Secondary	5.68 (5.13-6.28)	1.12 (0.98-1.28)
Higher	15.81 (17.76)	**1.48 (1.26-1.74)**
Pregnancy		
Number of ANC visits		
<5	Ref.	Ref.
≥5	6.58 (6.12-7.08)	**1.45 (1.32-1.60)**
Timing of first antenatal appointment		
≤ 3 months	Ref.	Ref.
4-6 months	0.37 (0.34-4.0)	0.97 (0.87-1.08)
≥ 7 months	0.26 (0.21-0.32)	1.06 (0.85-1.33)
ANC received at government/ municipal hospital	1.06 (0.98-1.14)	1.04 (0.93-1.16)
ANC received at Private hospital/maternity	2.89 (2.70-3.08)	**1.17 (1.05-1.30)**
Place of delivery		
Public sector [a]	Ref.	Ref.
Private sector [b]	1.97 (1.84-2.11)	**1.49 (1.35-1.64)**
Reproductive history		
Parity		
1 child	Ref.	Ref.
2 children	0.67 (0.63-0.72)	**0.82 (0.76-0.90)**
3+ children	0.17 (0.16-0.19)	**0.52 (0.47-0.58)**
Prenatal health		
Prenatal iron supplementation	3.77 (3.44 – 4.14)	1.03 (0.91-1.16)

[a] Government./municipal hospital, government dispensary, UHC/UHP/UFWC, CHC/Rural hospital/PHC, Sub-centre, Other public
[b] Private hospital/maternity, Other Private

Table 15 Characteristics of infants age ≤6 months with and without concomitant diarrhea and acute respiratory infection in the 2005-2006 India National Family Health Survey

	Infant does not have both ARI and diarrhea N=5,210 (%)	Infant has both ARI and diarrhea N=222 (%)	p- value
Mode of delivery			0.8144
Vaginal delivery	90.4	89.8	
Cesarean delivery	9.6	10.2	
Infant Outcomes			
Infant sex			0.0218
Male	49.6	59.4	
Female	50.4	40.6	
Year of birth			<.0001
2005	64.5	80.3	
2006	35.5	19.7	
Post-natal appointment within two months	7.5	14.4	0.1489
Breastfeeding			
Ever breastfed	99.2	99.8	0.0038
Initiated breastfeeding immediately	21.6	22.5	0.7983
Initiation of breastfeeding within one hour	33.6	38.7	0.2120
Currently breastfeeding	98.0	97.6	0.7308

Table 16 Crude and adjusted association between mode of delivery and concomitant diarrhea and acute respiratory infection among infants age ≤6 months in the 2005-2006 India National Family Health Survey

	Unadjusted OR (95% CI)	Adjusted OR * (95% CI)
Cesarean delivery vs vaginal delivery	0.79 (0.50-1.25)	0.91 (0.61-1.36)

*Model adjusted for IPTW predicting mode of delivery with: place of residence type, head of household caste, wealth index, highest education level, number of ANC visits, timing of first antenatal appointment, ANC received at government/municipal hospital or at private hospital/maternity, place of delivery, parity, prenatal iron supplementation

Table 17 Crude and adjusted associations between mode of delivery and adverse health outcomes among infants ≤6 months in the 2005-2006 India National Family Health Survey

	Cesarean vs Vaginal delivery	
	Unadjusted OR	Adjusted OR*
Diarrhea or respiratory infection (n= 1389)	0.90 (0.74-1.09)	0.91 (0.75- 1.10)
Diarrhea alone (n= 653)	0.99 (0.77- 1.28)	0.97 (0.76- 1.23)
ARI alone (n= 958)	0.83 (0.66 -1.04)	0.88 (0.71- 1.09)

*Model adjusted for IPTW predicting mode of delivery with: place of residence type, head of household caste, wealth index, highest education level, number of ANC visits, timing of first antenatal appointment, ANC received at government/municipal hospital or at private hospital/maternity, place of delivery, parity, prenatal iron supplementation

Table 18 Characteristics of neonatal deaths and living infants in the 2005-2006 India National Family Health Survey

	Child alive at interview N=35,748 (%)	Neonate died in first month N=753 (%)	P value
Mode of delivery			
Vaginal delivery	90.3	92.1	
Cesarean delivery	9.7	7.9	0.12
Infant Characteristics			
Infant sex			
Male	53.8	55.3	
Female	46.2	44.7	0.50
Year of birth			
2001	9.2	7.0	
2002	14.2	10.5	
2003	18.6	16.6	<.0001
2004	24.7	19.1	
2005	27.8	39.6	
2006	5.5	7.3	
Breastfeeding			
Ever breastfed	98.7	39.9	<.0001
Initiated breastfeeding immediately	23.6	22.0	0.5625
Initiation of breastfeeding within one hour	36.1	36.6	0.8821

Table 19 Crude and adjusted association between mode of delivery and neonatal mortality in the 2005-2006 India National Family Health Survey

	Unadjusted OR (95% CI)	Adjusted OR * (95% CI)
Cesarean delivery vs vaginal delivery	0.81 (0.63-1.03)	1.32 (1.04-1.67)

*Model adjusted for IPTW predicting mode of delivery with: place of residence type, head of household caste, wealth index, highest education level, number of ANC visits, timing of first antenatal appointment, ANC received at government/municipal hospital or at private hospital/maternity, place of delivery, parity, prenatal iron supplementation

6.0 CONCLUSION

6.1 PUBLIC HEALTH SIGNIFICANCE AND DIRECTIONS FOR FUTURE RESEARCH

The findings from our studies provide novel insight on CS delivery in India, addressing a knowledge gap on this topic in the epidemiologic literature. The overarching goal of this dissertation was to determine the factors associated with mode of delivery in India, and assess the impact of mode of delivery on adverse infant outcomes. First, we ascertained the individual level factors associated with cesarean delivery in a peri-urban cohort of 1,227 reproductive aged women in South India. Because this cohort were recruited into the study preconception or in first trimester, we had the unique advantage of evaluating pre-pregnancy and prenatal factors. We observed that the high CS rate is in part attributed to medical indications in labor and delivery in both multiparous and nulliparous mothers, including cephalo-pelvic disproportion, non-reassuring fetal heart rate pattern, and fetal breech position. Furthermore, in a subset of multiparous women with previous delivery records, prior CS delivery was a major predictor of recurrent CS, as has been found in other research studies. Our study population had access to good quality health care, which may not be the case throughout India. In an assessment of macro-level factors using nationally representative data from 2005-2006, we observed that socioeconomic and antenatal care factors were independently associated with CS delivery in India. Measures of maternal wealth, education, and access to private health care were found to increase the likelihood of a woman delivering her most recent birth by CS nationwide.

Second, we sought to elucidate whether infant health outcomes were associated with mode of delivery in India, as has been found in western countries. In both the peri-urban cohort and the nationwide survey sample we observed that cesarean delivery did not increase the likelihood of respiratory infection and/or diarrhea in infants age six months or younger. With our peri-urban cohort data we applied propensity score analysis to adjust for individual level pre-delivery factors associated with an increased likelihood of a mother delivering by CS. On a larger scale, in the national-level data set we applied propensity score analysis to adjust for socioeconomic and healthcare factors. In our assessment of the association between mode of delivery and neonatal mortality, a rare outcome, using the national-level survey data we observed a positive association. While our studies demonstrate that mode of delivery may not be a critical factor in determining the short-term health of infants in India, further exploration at the individual level is needed in order to determine whether cesarean delivery is a causal factor for neonatal mortality. This includes pregnancy specific details such as length of gestation, and prenatal and/or labor and delivery medical indications.

CS delivery rates continue to increase globally, making this surgical procedure a significant clinical and public health topic. With India poised to be the most populous country by 2050 with over 1 billion people, quantifying the effects of CS can help in prioritizing public health resources in order to prevent maternal and infant morbidity and mortality associated with CS. The joint effort being undertaken by the American College of Obstetricians and Gynecologists and the Society for Maternal-Fetal Medicine to safely reduce the CS rate in the US by preventing primary CS deliveries in low-risk pregnancies is a model that could be explored for application in India and other countries. [131] Strategies suggested to prevent primary CS include policy level changes to definitions of medical indications. [131] As we have also found that prior CS is a strong predictor for future CS delivery, prevention of primary CS should be a major research and public health objective internationally. In addition, future research is needed to assess how risk factors differ based on indication for CS delivery in India. Moreover, identifying country specific reasons for maternal preference for CS would allow for identification of modifiable factors as points of intervention associated with elective CS.

Previous research in Indian women found an association between Vitamin D deficiency or insufficiency and CS delivery. [52,53]Additional insight into the role of Vitamin D deficiency on cesarean delivery in the LIFE study may provide a point of maternal pre-pregnancy intervention to prevent primary CS. This could be explored using archived blood samples for a retrospective assessment of plasma levels of the biomarker 25-hydroxyvitamin D. As follow-up for the LIFE study is ongoing, there are additional opportunities to investigate this association prospectively. Further, as mode of delivery has not been found to be associated with the outcomes diarrhea or respiratory infection in the first six months of life in our studies, added research could elucidate the modifiable factors associated with these outcomes. Infant vaccination rates in the study were high, however the role of maternal vaccination and the acquisition of passive immunity and infant health can be explored, with additional information on maternal vaccination rates. While a positive association was found between CS delivery and neonatal mortality using national survey data, further research accounting for indication for CS and gestational age at birth would provide a more accurate assessment of the role of CS delivery on child mortality. Overall, the findings from our series of studies in Indian populations can also inform other low and middle income countries with increasing CS rates on the general impact of CS delivery on infant outcomes.

APPENDIX A: CESAREAN SECTION RATES IN INDIA BY STATE AND NFHS SURVEY

Table 20 Cesarean Section Rates in India from the National Family Health Surveys of 1992-1993, 1998-1999, and 2005-2006

Region	**State/ Territory**	**Percentage of live births in the three years preceding the NFHS delivered by caesarean section**		
		1992-93	**1998-99**	**2005-06**
	India Total	**2.6**	**7.1**	**9**
North	New Delhi	4.8	13.4	13.9
	Haryana	2	4.3	6.5
	Himachal Pradesh	1.2	5.1	14
	Punjab	4	8.2	18.2
	Uttar Pradesh, inc Uttaranchal	0.8	2.8	5
	Jammu & Kashmir	4.7	9.3	14
Central	Madhya Pradesh, inc Chhattisgarh	0.8	3.3	4.1
East	Bihar, inc Jharkhand	1	3	4.1
	Orissa	1.3	5	5.7
	West Bengal	3.9	10.3	10.1
Northeast	Arunachal Pradesh	0.8	5.4	3.4
	Assam	1.5	3.8	6.3
	Manipur	0.2	5.5	10
	Meghalaya	2.9	2.8	4.1
	Mizoram	2.3	10.8	6.1
	Nagaland	1.2	1.7	2.3
	Tripura	3.5	8	14.2
	Sikkim	-	7.3	13.4
West	Goa	14.1	20.2	27.2
	Gujarat	2.9	8.5	9.2
	Maharashtra	3.6	7.7	11.8
	Rajasthan	0.7	3.1	4.3
South	Andhra Pradesh	4.7	14.5	22.8
	Karnataka	3.5	11.1	16
	Kerala	14.2	29.3	31.1
	Tamil Nadu	7.5	15.8	21

APPENDIX B: CESAREAN SECTION RATES IN INDIA BY STATE AND NFHS SURVEY

MATERNAL AND MEDICAL PROVIDER PERCEPTIONS OF MODE OF DELIVERY IN AN INDIAN POPULATION

The attitudes, beliefs, preferences, and knowledge of vaginal compared to cesarean section delivery from a medical and cultural standpoint among the medical providers and mothers in the Longitudinal Indian Family hEalth (LIFE) study cohort are unknown, yet would provide insight into factors associated with mode of delivery in this population. Out of 1,169 live deliveries in the LIFE cohort through December 2015, 46% were via cesarean.

The objective of this pilot study was to elucidate perceptions of mode of delivery among the women enrolled in the LIFE study cohort, and obstetricians who practice at the MediCiti Institute of Medical Sciences (MIMS). In addition, to ascertain cultural and medical practice context regarding mode of delivery in this population. The findings contribute to the handful of qualitative studies conducted on the perceptions of the birth experience in India.

Study procedures

Mother’s Focus Groups

Two focus group discussions were conducted in July 2016 to assess women’s perceptions of mode of delivery. We used questions similar to those asked in the ‘Birth and Cesarean Specific’ section of the *Listening to Mothers Surveys*[132-134] in the USA, also incorporating questions relevant to the local culture. Trained, Telugu speaking focus group facilitators conducted the sessions, which were audio recorded following verbal consent of the participants. This study was approved by the SHARE INDIA ethics committee and the University of Pittsburgh Institutional Review Board.

Medical Provider Survey

A written survey was administered with physicians at MIMS based on the format of the "Optimal Cesarean Rates Survey".[67] The survey by Cavallaro et al. was developed to ascertain physicians' perception of the optimal rate of cesarean delivery worldwide, and how this differs from the WHO recommendation. The primary question for this survey was "What proportion of women should receive a cesarean for optimal fetal and maternal outcomes?" in a variety of obstetric scenarios.

Focus Group Discussion Results

Participant Demographics

27 women from Somaram and Dabil Pur villages (in Medchal Mandal) aged 22-35 years old participated in focus group discussions to ascertain maternal perception of mode of delivery. All women reported having at least one child, and 16 of them (59%) had at least one cesarean delivery. None of the participants had ever delivered at home. Majority of the women had delivered at MIMS or another private hospital.

Perception of Safety of Mode of Delivery

Women believe that vaginal delivery is safer than cesarean delivery. Although they considered cesarean less painful at the time of delivery. Those who had delivered by cesarean reported having difficulty conducting postpartum manual labor such as agriculture or construction work due to back pain, which they attributed to the spinal anesthesia injection.

Some women believe that cesarean deliveries are occurring at high rates for some private hospitals to earn money. Other reasons mentioned include pregnancy complications, and mother's lifestyle factors such as physical inactivity and poor diet. In addition, they mentioned that short physical stature, obesity, and low pain tolerance also contribute to the high cesarean rate.

Information about cesarean delivery is shared between friends and co-sisters, particularly those who have undergone cesarean deliveries. Age-mates are consulted for advice more than elders in their households.

Belief in Auspicious Days

Many women said they prioritize their health and safety over seeking auspicious days for delivery. Others said they knew of doctors who believed in auspicious days and advised them based on that. Some women mentioned conducting religious rites after the child is born.

Women who have previously delivered by cesarean

Most women believed that if their first delivery was a cesarean, then their second delivery would also be a cesarean. They mentioned that at some private practices they were not given a choice for mode of delivery from their physician. However, those with experience at MIMS and at government hospitals said that vaginal delivery is the first option, and cesarean is only performed if medically necessary. Family members help decide whether the cesarean delivery should be done after the physician has explained the medical condition.

Women were aware that if there is a short inter-pregnancy interval then delivering their subsequent pregnancy by vaginal delivery would be difficult if they initially had a cesarean. Many of them mentioned that if the space between pregnancies was less than five years then a repeat cesarean would be performed, per their doctor’s instructions/advice.

Physicians Survey Results

12 practicing obstetricians at MIMS were surveyed to assess their opinions of cesarean rates. Participants were required to have had experience performing cesarean deliveries within the last 5 years. Majority of the participants were women, age 30-39. All had completed their obstetrician training and gained their obstetrical experience in India, and one person in the United Kingdom. They also provided obstetric care in public, private for-profit, and private not-for-profit facilities, mainly at the regional referral hospital level.

In summary:

- 2/12 believed that 15-29% of all the deliveries at MIMS in one year were delivered by cesarean, the rest reported that the proportion is 30-49%.
- 9/12 do not believe that a mother should be able to choose her delivery date based on religious auspicious days.
- 4/12 answered that the optimal cesarean rate of all deliveries worldwide should be <15% for optimal maternal and fetal outcomes, 3/12 answered 16-20%, and 5/12 answered 21-30%.
- 7/12 answered that the optimal cesarean rate among women with a history of previous cesarean should be 50% or higher.
- 10/12 answered that the optimal cesarean rate among multipara, singleton cephalic delivery with no other risk factors at the onset of labor is 0-5%.
- The suggested optimal cesarean rate for nulliparous women raged from 0-5%, to 31-49%.

Conclusion

This sample of women enrolled in the LIFE cohort study had a preference for vaginal delivery over cesarean delivery, despite majority of them having delivered at least one child by cesarean. Physicians surveyed from MIMS indicated optimal cesarean rates >16%, which is above the WHO recommendation of 5-15% of births in each region. In terms of cultural factors that may be associated with the cesarean rate, auspicious days were not a factor in this population, neither for the women nor the physicians.

This project provided information on maternal knowledge and perception of mode of delivery in the LIFE study, which was previously unknown. Areas for patient education on the possibility for vaginal birth after cesarean (VBAC) were identified. Additional data on maternal and physician knowledge of the effects of cesarean delivery in the LIFE study should be attained.

APPENDIX C: STUDIES OF INFANT HEALTH OUTCOMES AND MODE OF DELIVERY

Table 21 Studies of Infant Health Outcomes and Mode of Delivery

Author, Year	Population Location	Study Design	N	Exposure(s)	Outcome	Covariates	Findings Estimate (95% CI)	Study strengths (+) and Weaknesses (-)
Lavin, 2017 [83]	Young Lives Study India and Vietnam	Longitudinal cohort	4, 026	CS delivery vs vaginal delivery	Caregiver reported asthma at 8 year olds	Breastfeeding, wealth index, child's sex, parity, low birthweight at term, geographic location, cooking fuel, ownership of livestock, household smoking, maternal age, housing quality and household size	Indian children aOR 2.6 (1.3-5.4) Vietnamese children aOR 2.0 (1.2-3.3)	+ Large sample size + Controlled for environmental risk factors -Did not control for parental asthma
Bentley, 2016 [79]	Singleton live births >33 weeks from 2001-2011 Australia	Population based retrospective	893, 360	Pre-labor CS vs Vaginal delivery + Gestational age at birth, and Formula vs breastfeeding	Acute gastroenteritis (AGE)	Parity, maternal age, maternal country of birth, SES, smoking, hypertensive disorders of pregnancy, diabetes, infant sex, Apgar score, birth weight, AGE in perinatal period, admittance to NICU, length of stay after birth, year of birth	Reference: Spontaneous vaginal birth at term fed with breast milk Term, pre-labor CS, formula fed: aHR 1.40 (1.32-1.48) Term, pre-labor CS, breastfed: aHR 1.19 (1.16-1.23)	+ Large sample size + Combined risk factors to assess exposure -No data on maternal antibiotic use -Only included severe AGE cases

Table 21 - Continued

Author, Year	Population Location	Study Design	N	Exposure(s)	Outcome	Covariates	Findings Estimate (95% CI)	Study strengths (+) and Weaknesses (-)
Kristensen, 2016 [78]	All births 1997-2012 Denmark	Population based cohort	750,569	elective CS and acute CS vs vaginal delivery	Mucosal immune related diseases (asthma, pneumonia, laryngitis, gastroenteritis, Crohn disease, ulcerative colitis, celiac disease, juvenile arthritis, diabetes, lymphatic leukemia, myeloid leukemia, malignant lymphoma, nonhematologic cancer)	Gestational age at birth, sex, birth weight, maternal age, maternal smoking during pregnancy, and complications during pregnancy (preeclampsia, eclampsia, hemorrhage, and hyperemesis)	Increased risk for all outcomes with elective and acute CS except Crohn disease, lymphatic leukemia, myeloid leukemia, malignant lymphoma, nonhematologic cancer, and diabetes	+ Large sample size +Ability to assess rare outcomes - Breastfeeding not assessed as confounder -Did not control for parental asthma
Yuan, 2016 [73]	Growing Up Today Study (GUTS) USA	Prospective cohort study	22, 068	CS delivery vs vaginal delivery	Obesity (BMI>30 in adults)	Maternal age at delivery, race, region, year of birth, prepregnancy BMI, maternal height, gestational diabetes. Preeclampsia, pregnancy induced hypertension, gestational age at delivery, birth weight, prepregnancy smoking, previous CS, child's sex, birth order	Overall: aRR 1.15, 95% CI 1.6-1.26 VBAC vs repeat CS: RR 0.69, 95% CI 0.53-0.83 CS vs Vaginal delivery among siblings: aRR 1.64, 95% CI 1.08-2.48	+ Large sample size -Outcome based on self-report + Could control for residual confounding in sensitivity analysis -Did not have information on antibiotic use -Study cohort factors limit generalizability

Table 21 - Continued

Author, Year	Population Location	Study Design	N	Exposure(s)	Outcome	Covariates	Findings Estimate (95% CI)	Study strengths (+) and Weaknesses (-)
Black, 2015 [84]	Term singletons born 1993-2007 Scotland, UK	Population based cohort	321, 287	Planned CS vs unplanned CS and vaginal delivery	Primary : asthma	Maternal age at delivery, maternal BMI, gestational age at delivery, carstairs decile, maternal smoking, year of delivery, child's sex, birth weight, maternal inhaler prescription, maternal type 1 diabetes, breastfeeding at 6 weeks	Planned vs unplanned CS HR 1.0 (0.9-1.12) Planned CS vs vaginal delivery 1.22 (1.11-1.34)	+ Large sample size + Only included primary pregnancies -Did not control for potential maternal confounders e.g. education, antibiotic use
Sevelsted, 2015 [77]	Danish national registries 1973-2012 Denmark	registry-based study	1.9 million	CS vs vaginal delivery	chronic immune diseases through 16 years old (asthma, systemic connective tissue disorders, juvenile arthritis, inflammatory bowel disease, leukemia, diabetes type 1, immune deficiencies, psoriasis, celiac disease)	Gender, parity, age, calendar time, season of birth, maternal age, maternal disease, birth weight	Increased risk for all outcomes except type 1 diabetes, psoriasis, and celiac disease	+ Large sample size + Long follow-up period + Controlled for maternal immune-related disease - Breastfeeding not assessed as confounder
Curran, 2015 [75]	Singleton live births 1982-2010 Sweden	Population based cohort	2, 697, 315 children 13, 411 sibling pairs	Emergency and elective CS delivery vs vaginal delivery	Autism spectrum disorders at 4 yrs. old in individuals and among siblings	Infant sex, maternal age, gestational age, parent citizenship, small for gestational age, large of gestational age, Apgar score, parity, welfare status, income, depression, bipolar disorder	Entire population: Elective CS aHR 1.21 (1.15-1.27) Emergency CS aHR 1.15 (1.10-1.20) Sibling pairs: Elective CS aHR 0.89 (0.76-1.04) Emergency CS aHR 0.97 (0.85-1.11)	+ Large sample size + Controlled for familial confounding with sibling pairs -Possible overrepresentation of severe ASD in inpatient registry

Table 21 - Continued

Author, Year	Population Location	Study Design	N	Exposure(s)	Outcome	Covariates	Findings Estimate (95% CI)	Study strengths (+) and Weaknesses (-)
Mueller, 2015 [74]	Northern Manhattan Mothers and Children Study New York City	Prospective cohort	436 mother-child pairs	CS vs vaginal delivery Maternal antibiotic use in pregnancy vs no use	Obesity at 7 years old	Exposure to smoke, education, income, public assistance, pre-gravid BMI, number of previous live births, gestational diabetes and hypertension, infant sex, birth weight, breastfeeding, ethnicity, maternal age	CS aRR 1.46 (1.08-1.98) Antibiotics aRR 1.84 (1.33-2.54)	+Accounted for maternal antibiotic use +Study obtained measures of outcome +Reduced confounding by only including non-smokers -Data on indication for antibiotic use not available -Study had high attrition
Almqvist, 2012 [85]	Children born between 1993 and 1999 Sweden	Population based cohort	87,555 sibling pairs	Emergency and elective CS delivery vs vaginal delivery	Report of asthma medication use and diagnosis	Gender, birth order, birth weight, gestational age, Apgar score, maternal age at delivery, smoking in pregnancy, mother living with child's father, mother's birth country, BMI	Asthma medication use in sibling pairs: Emergency CS aOR 1.19 (0.98-1.44) Elective CS aOR 0.85 (CI 0.68-1.05) Asthma diagnosis in sibling pairs: Emergency CS aOR 1.29 (0.84-1.99) Elective CS aOR 0.65 (0.42-1.02)	+ Large sample size + Controlled for familial confounding with sibling pairs - Breastfeeding not assessed as confounder -Did not control for parental asthma
Magnus, 2011 [86]	Norwegian Mother and Child Cohort Born 2001-2007 Norway	Retrospective cohort	37, 171	CS vs vaginal delivery	Wheezing, asthma, recurrent lower respiratory tract infection (LRTI)	BMI, education, maternal atopy, maternal chronic disease, smoking, preference for CS, pregnancy complications, maternal age, previous CS, parity, marital status, gender, birth weight, gestational age Intermediate variables: breastfeeding, day care	Wheezing aRR 1.03 (0.99-1.07) Asthma aRR 1.17 (1.03-1.32) Recurrent LRTI aRR 1.07 (0.92-1.25)	+ Large sample size + Many covariates + Assessed intermediate variables -Lacked information on severity -Differential follow-up in study by exposure status

Table 21 - Continued

Author, Year	Population Location	Study Design	N	Exposure(s)	Outcome	Covariates	Findings Estimate (95% CI)	Study strengths (+) and Weaknesses (-)
Renz-Polster, 2005 [76]	Kaiser Permanente Northwest Region medical records 1996-2000 Oregon, USA	Retrospective cohort	7,872 child-mother pairs	CS delivery vs vaginal delivery	Allergic diseases (asthma, allergic rhinitis, atopic dermatitis, and/or food allergy) in 3-10 year olds	Child's sex, age at diagnosis, birth weight, birth order, multiple gestation, antibiotic exposure, maternal age, ethnicity, education, marital status, mother's smoking status during pregnancy, use of allergic medications	Any allergic disorder overall: aOR 1.23 (1.06-1.43) Allergic rhinitis aOR 1.37 (1.14-1.63) Asthma aOR 1.24 (1.01-1.53)	+ Large sample size + Controlled for parental allergy - Breastfeeding not assessed as confounder
Laubereau, 2004 [80]	German Infant Nutritional Intervention program (GINI) Germany	Prospective cohort	865	CS vs vaginal delivery	GI symptoms, atopic dermatitis, nutritional allergen sensitization	Infant sex, parental allergy, birth order, pet ownership, gestational age, cord blood IgE, maternal age at birth, birth weight, smoking, parental education	Colicky abdominal pain at 4 months aOR 0.72 (0.48-1.1) Any diarrhea at 12 months aOR 1.46 (1.02-2.1) Atopic dermatitis to 5 nutritional allergens at 12 months aOR 2.06 (1.12-3.8)	+ Reduced confounding by restricting to exclusively breastfed children -Did not assess antibiotic use in pregnancy
Maitra, 2004 [87]	Avon longitudinal study of parents and children 1991-1992 UK	Population based longitudinal cohort	12, 367	CS vs vaginal delivery	Physician diagnosed atopy and asthma, parental report of asthma and wheezing	Maternal education, maternal smoking in pregnancy, maternal history of hay fever, ethnicity, other children in household, financial difficulties, house dampness, contact with cats, home overcrowding, breastfeeding duration, smoke exposure, birth weight, infant sex, gestational age, maternal age as delivery	Atopy aOR 1.04 (0.8-1.3) Parental report of asthma aOR 1.16 (0.9-1.5) Physician diagnosis of asthma aOR 1.14 (0.9-1.4) Wheezing aOR 0.95 (0.7-1.3)	+ Large sample size +Parental report of asthma supported by physician diagnosis + Controlled for many environmental factors -No measures on neonatal respiratory disorders

Table 21 - Continued

Author, Year	Population Location	Study Design	N	Exposure(s)	Outcome	Covariates	Findings Estimate (95% CI)	Study strengths (+) and Weaknesses (-)
Hakansson, 2003 [81]	Infants born 1984-1996 Sweden	Retrospective	192, 510	CS vs vaginal delivery	Childhood asthma and gastroenteritis (GE)	Year of birth, gender, maternal age, parity, education, maternal smoking	Asthma OR 1.31 (1.23-1.40) GE OR 1.31 (1.24-1.38) Both OR 1.74 (1.36-2.23)	+ Large sample size + Excluded mothers with asthma -Unable to control for environmental risk factors
Aye, 1991 [82]	Central Womens Hospital 1981-1986 Burma	Retrospective	1, 540	CS vs vaginal delivery	Admission to sick baby unit with diarrhea	None	RR 5.0 (4.5-5.5)	-Did not conduct multivariable analysis to control for other risk factors -Only included severe diarrhea cases

Abbreviations: aOR: Adjusted odds ratio; aRR: Adjusted relative risk; aHR: Adjusted hazards ratio; aIRR: Adjusted incidence rate ratio

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