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Identifying Mediators, Moderators and High-Risk Latent Classes of Preterm Birth and Low Birth Weight Among Pregnant Women in Rural Mysore, India

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IDENTIFYING MEDIATORS, MODERATORS AND HIGH-RISK LATENT CLASSES OF PRETERM BIRTH AND LOW BIRTH WEIGHT AMONG PREGNANT WOMEN IN RURAL MYSORE, INDIA

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Sandra Jelagat Kiplagat

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To: Dean Tomás R. Guilarte
Robert Stempel College of Public Health and Social Work

This dissertation, written by Sandra Jelagat Kiplagat and entitled Identifying Mediators, Moderators and High-Risk Latent Classes of Preterm Birth and Low Birth Weight Among Pregnant Women in Rural Mysore, India, having been approved in respect to style and intellectual content, is referred to you for judgment.

We have read this dissertation and recommend that it be approved.

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The dissertation of Sandra Jelagat Kiplagat is approved.

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DEDICATION

This dissertation is dedicated to my parents, Catherine and Josiah Kiplagat. Without their sacrifice, hard work, support, and most of all love, the completion of this work would not have been possible.

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ABSTRACT OF THE DISSERTATION

IDENTIFYING MEDIATORS, MODERATORS AND HIGH-RISK LATENT CLASSES OF PRETERM BIRTH AND LOW BIRTH WEIGHT AMONG PREGNANT WOMEN IN RURAL MYSORE, INDIA

by

Sandra Jelagat Kiplagat

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Professor Diana M. Sheehan, Major Professor

This dissertation examined the mediators, moderators, and high-risk latent classes of preterm birth (PTB) and low birth weight (LBW) among pregnant women in rural Mysore District, India. Secondary data analyses of a prospective cohort study conducted between 2011-2014 among 1540 women was performed to complete this dissertation.

In the first study, we examined the association between socioeconomic status (SES) and PTB and LBW. Latent class analysis (LCA) was performed to assess sociodemographic patterns of high-risk pregnant women based on education, income, marital status, primigravida status and number of children. We identified four distinct classes, Class 1 “low SES/early marriage/multigravida/1 child or more”, Class 2 “low SES/later marriage/primigravida/no children”, Class 3 “high SES/later marriage/multigravida/1 child or more”, and Class 4 “high SES,/later marriage/primigravida/no children”. Women in Class 1 (aOR: 1.77, 95% CI: 1.05-2.97) and Class 2 (aOR: 2.52, 95% CI: 1.51-4.22) had higher odds of PTB and LBW, respectively.

In the second study, we examined the moderating role of Accredited Social Health Activists (ASHA) home visits and ASHA-accompanied antenatal care visits (ANC) on the relationship between sociodemographic latent classes (identified in the first study) and PTB and LBW. Women in Class 1 and Class 3 who never or rarely had ASHA-accompanied ANC visits had higher odds of PTB (aOR: 2.62 95% CI: 1.12-6.12, aOR: 3.47 95% CI:1.31-9.15, respectively).

Lastly, we examined the mediating role of anemia in the relationship between low SES and PTB and LBW. Employing LCA on relevant SES measures i.e., income, education, occupation and early marriage, we identified two distinct classes: Class 1 "low SES and early marriage" and Class 2 "high SES and later marriage". Findings suggested a significant direct effect of Class 1 on LBW (adjusted odds ratio [aOR]: 2.11, 95% confidence interval [CI]: 1.43-3.45), but no significant indirect effects (aOR: 0.99, 95% CI: 0.95-1.00.)

In conclusion, belonging to a low SES class emerged as the strongest predictor of PTB and LBW, and tailored interventions for this demographic group are needed to reduce socioeconomic inequities. While our study did not observe anemia as a significant mediator, future studies should explore other mediators such as infections and inflammatory markers. Further, strengthening the ASHA program is vital for quality-care home visits and uptake of ANC visits, which may ultimately reduce PTB and LBW in rural India.

TABLE OF CONTENTS

ABBREVIATIONS AND ACRONYMS

aBIC	Adjusted Bayesian Information Criterion
AIC	Adjusted Information Criterion
ASHA	Accredited Social Health Activists
aOR	Adjusted Odds Ratio
ANC	Antenatal Care
BIC	Bayesian Information Criterion
CI	Confidence Interval
INR	Indian Rupees
LBW	Low Birth Weight
LCA	Latent Class Analysis
NFHS	National Family Health Survey
NMR	Neonatal Mortality Rate
NRHM	National Rural Health Mission
OR	Odds Ratio
PHRII	Public Health Research Institute of India
PTB	Preterm Birth
SCIL	Saving Children Improving Lives
SES	Socioeconomic Status
USD	United States Dollar
WHO	World Health Organization

INTRODUCTION

Birth weight and gestational age are important indicators for neonatal health and infant development as they reflect the fetal development progression throughout pregnancy. Low birth weight (<2500 g) and preterm birth (<37 weeks of completed gestation) are the leading causes of neonatal morbidity and mortality. Each year, nearly 20 million babies are born low birth weight, and approximately 15 million babies are born preterm globally (World Health Organization 2014b, 2018a). Low birth weight constitutes 60-80% of neonatal deaths (World Health Organization 2018a), while prematurity accounts for nearly 35% of all neonatal deaths and is ranked as the leading cause of death for children under 5 years of age worldwide (World Health Organization 2018a; Liu et al. 2016). In addition to mortality, these adverse birth outcomes have also led to short-term and long-term sequelae (Patel 2016). Short-term outcomes may include respiratory conditions such as respiratory distress syndrome and bronchodysplasia, necrotizing enterocolitis, neonatal sepsis, difficulty in feeding, and poor body temperature regulation (Patel 2016; Goldenberg and Culhane 2007). Moreover, low birth weight and preterm birth can lead to lifelong and chronic diseases such as neurological impairments, visual and hearing problems, cardiovascular, renal and metabolic defects after birth (Mwaniki et al. 2012; Patel 2016; Blencowe et al. 2013; Goldenberg and Culhane 2007; Grandi et al. 2019). Further, the economic and social costs of preterm birth in the most recent data available were approximately 26.2 billion dollars in the United States and may be significantly higher in other countries (Behrman and Butler 2007). The costs are associated with a prolonged stay in neonatal intensive care unit, ongoing health-care and educational needs which may result in a physical, emotional, and financial toll on family members (Blencowe et al. 2013).

Low birth weight constitutes infants with preterm birth and fetal growth restrictions (Goldenberg and Culhane 2007; World Health Organization 2018a). On the other hand, preterm birth may occur spontaneously (spontaneous preterm birth or preterm premature labor rupture of membranes) or be due to provider-initiated preterm birth (Blencowe et al. 2013). The World Health Organization, classified preterm birth into extremely preterm (<28 weeks), very preterm (28-32 weeks), and moderate-late preterm births (32-37 weeks) (World Health Organization 2018a). The etiology and mechanisms of preterm birth and low birth weight are poorly understood. Typically, 50% of preterm births do not have a specific risk factor reported (Muglia and Katz 2010). Determinants that may increase the risk of these adverse birth outcomes include clinical, biological, behavioral, environmental, and sociodemographic factors. Sociodemographic factors including younger age (less than 16 years) or older age (more than 40 years) at pregnancy, low socioeconomic status (SES), lower education levels, and early age at marriage (Fall et al. 2015; Vahdaninia, Tavafian, and Montazeri 2008a; Hidalgo-Lopezosa et al. 2019; Raj et al. 2010b) are contributing factors to preterm birth and low birth weight. Subsequently, women with low SES are more likely to have limited access to healthy nutrition, use substances including smoking and alcohol, have inadequate antenatal care, and have limited access to quality obstetric services, (Ghimire et al. 2018a; Gravett, Rubens, and Nunes 2010; Heredia-Olivera and Munares-García 2016), which inadvertently contributes to an increased risk of preterm birth and low birth weight. Moreover, chronic diseases such as anemia (Young et al. 2019; Parks et al. 2019) diabetes (Kong et al. 2019; Köck et al. 2010), and hypertensive disorders during pregnancy (Catov et al. 2008; Gilbert, Young, and Danielsen 2007) are determinants of preterm birth and low birth weight. Lastly, infectious diseases such as HIV, bacterial vaginosis, urinary tract infections, and inflammatory markers such as prostaglandins, cytokines and proteinases have been associated with preterm birth (Gravett, Rubens, and Nunes 2010; Tchirikov et al. 2018).

The majority of the risk factors have been identified from studies in high-income settings (Goldenberg and Culhane 2007; Goldenberg et al. 2008). However, there is an increasing need to understand the key determinants and prevalence of preterm birth and low birth weight particularly in low-income, high burden settings. According to the 2019 Indian Healthy Newborn Network report, 14% of births in India are preterm (Chawanpaiboon et al. 2019), and 28% of births are low birth weight (Tellapragada et al. 2016), proportions which are among the highest in the world. Annually, 3.5 million babies in India are born preterm, and almost 360,000 infants die as a result of preterm birth related complications (Every Preemie Scale 2019). India has the highest number of neonatal deaths in the world, with nearly 750,000 reported in 2013 (Liu et al. 2016). Adverse birth outcomes are even more common in rural regions among tribal and marginalized communities in India. In 2016 alone, Mysore, the second largest district in the Southern State of Karnataka, had an infant mortality rate of 33 per 1,000 live births in rural regions of the state, while the state of Karnataka had an infant mortality rate of 33 per 1,000 live births in rural areas compared to 20 per 1,000 live births in urban areas (International Institute of Population Health Sciences 2016). However, there is dearth of data on the causes of infant mortality as well as the prevalence and predictors of preterm and low birthweight in rural Mysore. Possible reasons may include inconsistent data reporting for gestational age, lack of data records for home births, and lack of operational civil registration and vital statistics (CRVS) system in place highlighting the stark disparities in data accuracy of these measures between high-resource and low-resource settings (Blencowe et al. 2019).

Given the paucity of studies in rural populations in India, there is an urgent need to elucidate the driving mechanisms for these poor birth outcomes. While previous studies have assessed the risk factors for preterm birth and low birth weight in India (Undela et al. 2019a; Raj et al. 2010a) largely in hospital settings, large-scale studies, and in high-risk states (Ahankari et al. 2017; Kumari et al. 2019; Sureshbabu et al. 2021; Banerjee, Singh, and Chaurasia 2020), limited studies have focused on marginalized and tribal communities in rural India which bears a disproportionate burden of adverse birth outcomes (International Institute of Population Health Sciences 2016). Secondly, some researchers have utilized large cohort studies in high-income countries (Delnord et al. 2017; Lui et al. 2019) to highlight the risk factors and probable causal mechanisms. However, these risk factors and causal mechanisms have not been studied in community-based rural settings in India. Thirdly, prior studies have utilized traditional multivariable methods such as logistic regression to examine the predictors of preterm birth and low birth weight (Ahankari et al. 2017; Kumari et al. 2019; Sureshbabu et al. 2021). Few studies have employed novel analytical approaches to examine the complex causal pathway of risks for pregnant women in rural India within tribal communities. Specifically, approaches such as latent class analysis, and mediation analysis have been used to study preterm birth and low birth weight predominantly in high-income settings

(Hendryx, Chojenta, and Byles 2020; Tian et al. 2018; Shaw, Herbers, and Cutuli 2019). Furthermore, scant studies have evaluated evidence-based interventions such as the roles of community health workers on reducing preterm birth and low birth weight (Tripathy et al. 2016). Implementing diverse methodological approaches has the potential to improve the understanding of the causal mechanisms and to identify target populations of high-risk pregnant women. This information can assist in the implementation of evidence-based approaches addressing preterm birth and low birth weight among rural populations so that the Sustainable Development Goals (SDGs) put forward by the United Nations can be met. These include reducing newborn mortality to no more than 12 per 1,000 live births in every country and reducing under-five mortality to no more than 25 per 1,000 live births (SDG 3.2) (World Health Organization 2018b).

One of the many initiatives to address the high neonatal burden was the launch of the National Rural Health Mission India (NRHM), first established in 2005. The objective of this program was to strengthen the healthcare systems as well as increase institutional delivery access and ANC services coverage in in rural regions in India (Dhingra and Dutta 2011). One key strategy was the implementation of the Accredited Social Health Activists (ASHA) in 2006, a community health worker program, serving as a connector between the healthcare system and the general public (National Health Mission 2020). The key responsibilities of the ASHA program were counseling and educating pregnant women, registering women for ANC visits, offering nutritional support, supporting healthcare service delivery through home visits. Previous studies have evaluated that ASHAs have been beneficial in expanding ANC visits, increasing facility-based deliveries, and reducing perinatal deaths (Agarwal et al. 2019; Paul and

Pandey 2020; Tripathy et al. 2016). However, the role of ASHAs on adverse birth outcomes such as preterm birth and low birth weight in rural India have not been thoroughly explored.

Therefore, the overall objective of this study was to identify mediators, moderators, and classes of women at high risk of having a baby with preterm birth or low birth weight in rural Mysore District, India. To accomplish the main objective, we performed secondary data analysis from a prospective cohort study from the Public Health Research Institute of India. The first study aimed to examine the SES patterns and assess the association of these patterns on preterm birth and low birth weight. The second study aimed to identify the moderating role of Accredited Social Health Accredited (ASHA) home visits and ASHA-accompanied Antenatal Care (ANC) visits on the relationship between sociodemographic latent classes of pregnant women (identified in the first study) and preterm birth and low birth weight infants. Lastly, in the final study, we examined the mediating role of anemia in the relationship between relevant SES measures and preterm birth and low birth weight. This study has the potential to identify high-risk groups of pregnant mothers who will require more medical attention and to assist in the integration of targeted and tailored interventions to promote healthy pregnancies and thriving infants in rural India.

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MANUSCRIPT 1

Sociodemographic Patterns of Preterm Birth and Low Birth Weight among Pregnant Women in Rural Mysore District, India: A Latent Class Analysis

Abstract

Background

Few studies have utilized person-centered approaches to examine co-occurrence of risk factors among pregnant women in low-and middle-income settings. The objective of this study was to utilize latent class analysis (LCA) to identify sociodemographic patterns and assess the association of these patterns on preterm birth (PTB) and/or low birth weight (LBW) in rural Mysore District, India.

Methods

Secondary data analysis of a prospective cohort study among 1540 pregnant women was conducted. Latent class analysis was performed to identify distinct group memberships based on a chosen set of sociodemographic factors. Binary logistic regression was conducted to estimate the association between latent classes and preterm birth and low birth weight

Results

Four latent classes were identified. Women belonging to Class 1 "low socioeconomic status (SES)/early marriage/multigravida/1 child or more", had higher odds of preterm birth (adjusted Odds Ratio (aOR): 95% Confidence Intervals (CI): 1.77, 95% CI: 1.05-2.97) compared to women in Class 4 "high SES/later marriage/primigravida/no children".

Women in Class 2 "low SES/later marriage/primigravida/no children" had higher odds of low birth weight (aOR: 2.52, 95% CI: 1.51-4.22) compared to women in Class 4. Women <20 years old vs ≥ 25 years old (aOR: 2.00, 95% CI: 1.08-3.71) and hypertension (>140/>90 mm/Hg) (aOR: 2.28, 95% CI: 1.02-5.07) were significant determinants of preterm birth. Furthermore, women with a previous low birth weight infant had higher odds of delivering a subsequent low birth weight infant (aOR: 2.15, 95% CI: 1.40-3.29).

Conclusion

Overall study findings highlighted that women belonging to low socioeconomic status, and multigravida women had increased odds of preterm birth and low birth weight infants. Targeted government programs are crucial in reducing inequalities in preterm births and low birth weight infants in rural India.

Key words: latent class analysis, low birth weight, pregnancy, preterm birth, risk factors

Introduction

While medical innovations and government policies have advanced neonatal health, there remains disproportionately high rates of adverse birth outcomes globally (World Health Organization 2018a). The greatest burden of preterm births (<37 weeks gestation) and low birth weight infants (<2,500 grams) occurs in low-and middle-income countries (LMICs) where more than 80% of preterm births and nearly 91% of low birth weight babies are born promoting a sense of urgency (Chawanpaiboon et al. 2019; Blencowe et al. 2019). Nearly ten million low birth weight babies (almost half of the global burden) and approximately 9 million preterm infants are born annually in Southern Asia (Blencowe et al. 2019; Blencowe et al. 2012). More specifically, India has the highest number of preterm births worldwide with approximately 3.5 million preterm births and 8 million low birth weight infants born annually (Blencowe et al. 2012; World Health Organization 2004). Additionally, the proportions of all births that are preterm (13%) and low birth weight (40%) in India remain among the highest in the world (Chawanpaiboon et al. 2019; Lawn et al. 2014; World Health Organization 2004). Consequently, India currently accounts for the highest number of neonatal mortality worldwide, with 779,000 deaths annually (Lawn et al. 2014). The neonatal mortality rates in India are even higher in rural areas with 31 neonatal deaths per 1000 live births compared to 15 per 1000 live births in urban areas (Sankar et al. 2016).

Infants born prematurely are vulnerable and are at an increased risk of infections including neonatal sepsis, unconjugated hyperbilirubinemia, respiratory distress syndrome, difficulty in feeding, and poor body temperature regulation (World Health Organization 2018a, 2016; Moutquin 2003; Blencowe et al. 2013). Preterm birth complications are the leading cause for deaths among children under 5 years of age (Liu et al. 2016). Low birth weight has been associated with acute and chronic health conditions including a lower intelligence quotient, neurological impairments, and stunted growth in childhood (World Health Organization 2014a). Additionally, they are at higher risk for developing hypertension and cardiovascular disease during adulthood (World Health Organization 2014a). Attempts to elucidate the etiology of preterm birth and low birth weight remain unclear but include clinical, biological, behavioral, and sociodemographic factors. Studies suggest that maternal anemia, diabetes, smoking and prior preterm birth are predictors of preterm birth and low birth weight (Liabsuetrakul 2011; Parks et al. 2018; Oaks et al. 2019; Andraweera et al. 2019; Grandi et al. 2019; Vahdaninia, Tavafian, and Montazeri 2008b; Su et al. 2018).

The majority of studies that have identified risk factors for preterm birth and low birth weight have used multivariable analyses (Apte et al. 2019; Hidalgo-Lopezosa et al. 2019; Rai et al. 2019). While these approaches can identify risk factors, they fail to examine the co-occurrence of risk factors that may further exacerbate adverse birth outcomes (Jobe-Shields et al. 2015; Hendryx et al. 2014). Person-centered approaches such as latent class analysis (LCA) identify and classify homogeneous unobserved sub-groups characterized by individuals with similar co-occurring risks (Lanza et al. 2018). The majority of the studies have employed LCA on either low birth weight or preterm birth distinctly and in high-income countries such as the US and Australia and have explored risk factors including behavioral risk factors, sociodemographic indicators and chronic diseases (Hendryx et al. 2014; Tian et al. 2018; Shaw, Herbers, and Cutuli 2019; Hendryx, Chojenta, and Byles 2020). However, the complexity of sociodemographic factors and maternal obstetric outcomes has not been explored in LMICs using LCA, which remains critical since preterm and low birth weight births largely occur in these settings. Further, no studies have examined the impact of sociodemographic factors and clinical variables using LCA among rural and tribal populations in rural India. Therefore, the objective of this study was to utilize LCA to identify sociodemographic patterns and assess the association of these patterns on preterm delivery and/or low birth weight among pregnant women in rural Mysore District, India.

Materials and Methods

Study Setting

According to the 2011 census, Mysore District had a total population of 3,001,027 of which 1,489,527 were females ('Mysore District : Census 2011 data'). Majority of the residents (58.5%) lived in rural villages. The male literacy rate (78.5%) was higher than the female literacy rate (67.1%) ('Mysore District : Census 2011 data'). Nearly 87.7% of the population self-identified as Hindu, 9.7% as Muslim, and 1.3% as others ('Mysore District : Census 2011 data'). The scheduled caste population comprised 17.9% of the population, while the scheduled tribes were 11% of the total population. The languages commonly spoken in Mysore are Kannada (81.2%), Urdu (8.6%), and Telugu (3.3%) ('Mysore District : Census 2011 data'). In 2016, Mysore, the third largest district in the South Indian state of Karnataka, had an infant mortality rate of 33 per 1,000 live births in rural regions of the state, while the state of Karnataka had an infant mortality rate of 28 per 1,000 live births (International Institute of Population Health Sciences 2016).

Study Population and Design

The original study included a total of 1,948 pregnant women living in Mysore district who were enrolled in the Saving Children Improving Lives (SCIL) project. This was a prospective cohort study conducted between 2011 and 2014 to examine the feasibility of integrated antenatal care and HIV testing using mobile clinics in rural Mysore District, Karnataka as described in the protocol by Kojima et al (Kojima et al. 2017). The protocol for the study was reviewed and approved by the Institutional Review Boards of Florida International University and Public Health Research Institute of India.

The eligibility criteria included women who were 18 years and older and living in the Mysore sub-district for more than six months. Based on the eligibility criteria, the total sample size was 1678 participants. If the woman met the eligibility criteria, she underwent an informed consent process in the local language of *Kannada* in a private space. Participants who elected to participate in the interview completed an interviewer-administered questionnaire conducted by research staff of Public Health Research Institute of India (PHRII). The questionnaire comprised of sociodemographic, medical, current reproductive history, and clinical laboratory examinations for sexually transmitted infections during pregnancy.

This study was a cross-sectional analysis nested within the parent study, the SCIL project. The predictor measures were collected at baseline (at enrollment into the study), and the study outcomes were collected during the first follow-up (within 15 days after delivery). In our study, 8% of the sample was excluded due to no known date of last menstrual period or missing dates on deliveries (n=40) and mothers whose infants died before birth (n=98). The total number of participants included in the study were 1,540.

Outcome and Predictor Variables

Outcomes

The outcomes in our study were preterm birth and low birth weight. We defined low birth weight as an infant born weighing less than 2500 grams (World Health Organization 2004). Based on the last menstrual period, we defined preterm births as live births born before 37 weeks of gestation (World Health Organization 2018a).

Predictor Variables

The variables included pregnant woman's education, partner's education, household income, age at marriage, primigravida, and living children in the household. Education was categorized as primary education or less (≤8 years), secondary education (9-10 years) and upper secondary education (>10 years). Household income was categorized as low income ≤4,000 Indian Rupees (INR) (approximately USD 54.7 with 1 USD = 58.9 INR during the data collection period), middle income as 4001-10,000 INR, and high income as ≥ 10,000 INR. Age at marriage was categorized into <18 years old, or ≥18 years old. Living children in the household was dichotomized as yes or no. Covariates included age, delivery location categorized as home, public health institution (sub-center/primary health center/ district health) and private institution (maternity hospital/private nursing home). These measures were selected based on prior literature on maternal obstetric factors. (Blencowe et al. 2013) Age was categorized as <20 years, 20-24 years and ≥ 25 years. Maternal obstetric factors included baseline sexually transmitted infections (STIs) (binary variable with "yes" or "no"), previous stillbirth or neonatal losses (binary variable with "yes" or "no"), history of spontaneous abortion (binary variable with "yes" or "no"), history of induced abortion (binary variable with "yes" or "no"), exposure to passive smoking indoors (binary variable with "yes" or "no"), and history of hypertension (binary variable with "yes" or "no"). Anemia status levels were labeled as normal, mild, and moderate/severe based on the hemoglobin levels of 11.0g/dl or higher, 10-10.9 g/dl, and ≤10.0 g/dl respectively. Hypertension categories were based on blood pressure levels as follows: normal (<120/80 mm Hg), pre-hypertension (120-

139 mm Hg systolic or 80-89 mm Hg diastolic) and hypertensive categories (≥140 mm Hg systolic or ≥90 mm Hg diastolic).

Statistical Analysis

We conducted latent class analysis using the SAS/STATv14.2 software, PROC LCA to identify and classify homogeneous unobserved sub-groups of pregnant women based on a chosen set of sociodemographic indicators including pregnant woman's education, partner's education, age at marriage, primigravida status, living children in the household, and total monthly household income (Lanza et al. 2018; Nylund-Gibson and Choi 2018). First, we employed a model comparison approach by testing unconditional models without covariates in the LCA. We assessed the model fit using a series of 2 through 6 latent classes. Second, the appropriate number of latent classes were selected based on the Bayesian Information Criterion (BIC), Adjusted Bayesian Information Criterion (aBIC), Adjusted Information Criterion (AIC), entropy values and the interpretability of latent classes. Lower BIC, aBIC, and AIC indicated a better model fit (Nylund, Asparouhov, and Muthén 2007). An entropy value closer to 1.0 represented a better distinction of the latent classes (Lanza et al. 2018).

After we chose a final class set based on BIC, aBIC, AIC, every individual was assigned to the latent class based on the highest posterior probability of membership. Subsequently, we generated descriptive statistics for the explanatory variables used in the LCA and the latent classes. Univariate analyses were conducted using chi-square tests to examine the associations between latent classes and the covariates. Finally, binary logistic regression was applied to estimate the association between latent classes and the outcome measures (i.e., preterm birth and low birth weight) while controlling for maternal obstetric covariates. The results were presented as odds ratios and associated 95% confidence intervals.

Results

Sample Characteristics

Table 1 displays the characteristics of the participants. Approximately 23.4% of the pregnant women were aged <20 years, 63.8% were aged 20-24 years, and 12.7% were aged 25 years and older. Nearly 40% of the pregnant women had received a primary education or less, while more than half (53.1%) of their partners had primary education or less. Nearly 37% of the women were primigravida, and more than half of the participants had living children in the household. Approximately a third of the women reported that the total household income was less than 4000 Indian Rupees (INR). The majority of the births were institutional deliveries with 51.8% of the women giving birth at a sub-center/primary health center/district health and 47.2% giving birth at a maternity hospital/private nursing home; only 0.8% of births were at the women's home. Nearly 7.3% (95% confidence intervals (CI): 6.0%-8.2%) of the women were diagnosed as having a baseline STI. Approximately 10% of the participants reported a history of spontaneous abortion, and 3.2% reported a history of induced abortion. Almost 20% were exposed to passive smoking in the house, and 18.3% reported having delivered a previous low birth weight infant. More than 75% of the women were diagnosed with anemia (20.3% mild and 55.6% moderate/severe). Nearly 2% of the women reported a history of hypertension during their last pregnancy. In addition, 37.6% of the women were diagnosed with blood pressure considered pre-hypertensive, and 2.7% had hypertensive levels at baseline. Low birthweight occurred in nearly 14% (95% CI: 12.1%-15.7%) of deliveries, while preterm birth occurred in 12% (95% CI: 10.6%-13.9%) deliveries.

Latent Class Analysis

Based on the model fit parameters, the model with four latent classes was selected as the best fitting and most parsimonious model with lowest BIC (445.41), adjusted BIC (321.52), and AIC (237.17) and distinct class separation based on entropy value of 0.75. While the 3-class model offered greater entropy, no major differences were observed between the 3-class and 4-class entropy values at 0.80 and 0.75, respectively. Sensitivity analysis was also performed comparing the 3-class and 4-class models, and we observed similar findings. Moreover, adding classes beyond the 4-class model conferred minor improvements in accuracy and model fit. Hence, a 4-class model was chosen based on its model fit statistics and the interpretability of classes.

Class 1 (46.0%), the largest class in our study, was labeled as “low socioeconomic (SES)/early Marriage/Multigravida/1 Child or More”. Class 1 was characterized by the majority of pregnant women and their respective partners having primary education or less, more likely to have a monthly household income <4000 INR, marriage <18 years of age, multigravida, and more likely to have children (Table 1). Class 2 (23.0%) was labeled as “low SES/later marriage/primigravida/no children.” This class was characterized by the majority of pregnant women and their respective partners having primary education or less, more likely to have a monthly household income of <4000 INR, more likely to be married after 18 years of age, primigravida and no children. Class

3 (13.9%) was labeled as “high SES/later marriage/multigravida/1 child or more.” Class 3 was characterized by the majority of pregnant women and their respective partners having at least an “upper secondary education”, more likely to have a monthly household income of ≥4000 INR, more likely to be married after 18 years of age, multigravida and living children in the household. Class 4 (17.0%) was labeled as “high SES/later marriage/primigravida/no children”. Class 4 was characterized by the majority of pregnant women and their respective partners having upper secondary education, more likely to have a monthly household income of ≥4000 INR, more likely to be married after 18 years of age, primigravida and no children. Class 4 was used as the referent group.

Table 2 displays the results of univariate analyses and comparisons between the maternal obstetric covariates and the latent classes. Maternal obstetric covariates were significantly associated with the latent classes except for anemia status and hypertension. The proportion of women reporting prior adverse maternal obstetric outcomes i.e., previous still birth or neonatal loss, prior history of spontaneous abortion, prior history of induced abortion, anemia, exposure to passive smoking indoors, prior low birth weight was highest among women in Class 1. Women in class 1 were also characterized with the highest proportion among women aged 20-24 years old. The proportion of women reporting baseline STI levels was highest in Class 2. In addition, the majority of these women was younger than 20 years old. The proportion of women reporting both prior adverse maternal obstetric outcomes and chronic diseases including moderate or severe levels of anemia and history of hypertension was highest in Class 3. Moreover, these women were likely to be 25 years and older. The proportion of women with prior and current adverse maternal obstetric outcomes and chronic diseases was lowest in Class 4.

Table 3 displays the crude and adjusted odds ratio (OR) and 95% CI for the relationship between latent classes and preterm birth and low birth weight. When compared with women in Class 4, women in Class 1 had higher crude odds for preterm birth (OR: 1.79, 95% CI: 1.10-2.91). After adjusting for the covariates, women in Class 1 had higher odds for preterm birth (adjusted OR [aOR]: 1.77, 95% CI: 1.05-2.97) compared with women in Class 4. In addition, women less than 20 years old were twice as likely to have a preterm birth (aOR: 2.00, 95% CI: 1.08-3.71). Moreover, hypertension (>140/>90 mm/Hg) was also a significant determinant of preterm birth (aOR: 2.28, 95% CI: 1.02-5.07). Women with mild anemia at baseline also had significantly lower odds of preterm birth compared to those with normal hemoglobin levels (aOR: 0.58, 95% CI: 0.33-0.98).

When compared with women in Class 4, women in Class 1 (OR:1.75, 95% CI: 1.08-2.84) and Class 2 (OR: 2.83 95% CI: 1.71-4.71) had higher crude odds for low birth weight. Moreover, pregnant women with history of neonatal loss or still birth (OR: 1.92, 95% CI: 1.04-3.54) and passive smoking exposure had higher crude odds for low birth weight (OR: 1.40, 95% CI: 1.03-2.07). The multivariable model showed that women in Class 2 had higher odds of low birth weight (aOR: 2.50, 95% CI: 1.49-4.21) compared to women in Class 4 (Table 3). Moreover, pregnant women with a previous low birth weight had higher odds of low birth weight (aOR: 2.15, 95% CI: 1.40-3.29) compared to women without any previous low birth weight. There was no significant association with baseline anemia.

Discussion

This study employed LCA to identify sociodemographic patterns and assessed the role of these patterns in determining preterm delivery and/or low birth weight among pregnant women in South India. The LCA identified four subgroups of women characterized by distinct sociodemographic profiles, with approximately 46% representing "low SES/early marriage/multigravida/1 child or more". Women belonging to Class 1 "low SES/early marriage/multigravida/1 child or more" had higher odds of a preterm delivery compared to the referent class 4 "high SES/later marriage/primigravida/no children". In addition, women belonging to Class 2 "low SES/later marriage/primigravida/no children" had higher odds of delivering a low-birth-weight baby compared to Class 4. Women with a history of having delivered a previous infant with low birth weight also had greater odds of delivering a subsequent infant with low birth weight.

Our study findings indicate that low SES conveyed significant risk to preterm birth and low birth weight among rural pregnant women. The most notable differences observed among Class 1, Class 2 and Class 4 are low SES compared to high SES. Several studies have corroborated that sociodemographic factors stemming from low maternal education, and low household wealth are determinants of adverse birth outcomes (Apte et al. 2019; Blumenshine et al. 2010; Hidalgo-Lopezosa et al. 2019; Rai et al. 2019; Tian et al. 2018; Kader and Perera 2014). Overall findings highlight that all the classes that comprised primarily of women with low SES had higher crude odds of preterm birth and low birth weight. After controlling for maternal obstetric characteristics, Class 1 and Class 2 remained statistically significant for preterm birth and low birth weight respectively. Previous LCA studies have established socioeconomic characteristics as determinants of either low birth weight or preterm birth in high-income settings (Tian et al. 2018; Shaw, Herbers, and Cutuli 2019; Hendryx et al. 2014; Hendryx, Chojenta, and Byles 2020). A recent systematic review noted that socioeconomic disparities remained the most significant predictor of adverse perinatal outcomes including preterm birth, low birth weight and small for gestational age (Blumenshine et al. 2010). It is speculated that pregnant women with high SES have reduced odds of delivering babies born with adverse birth outcomes due to increased access to antenatal care, improved health literacy, and nutritional behavior (Blumenshine et al. 2010).

In addition, the women characterized in Class 2, married over the age of 18 years old and were primigravida. It is possible that these women who are pregnant for the first time have unknown underlying factors. Additionally, these women may not be connected with antenatal care services and may lack prior pregnancy experience compared to multigravida women. Earlier studies have supported the finding that primigravida is associated with low birth weight (Ahankari et al. 2017; Kamala et al. 2018). A case-control study in Southern India indicated that primigravida was associated with increased odds of low birth weight (Johnson et al. 2016). More importantly, the compounding of risks in Class 2 of low SES, primigravida and later marriage has been shown to further exacerbate low birth weight. Notably, Class 1 was significant in the adjusted models for preterm birth among women belonging to low SES and marrying early. A distinct characteristic is that the women in Class 1 were multigravida, and not pregnant for the first time. While these women may have been connected to antenatal services during previous pregnancies, women in Class 1 reported the highest prior adverse maternal obstetric outcomes among the classes. Our study findings have confirmed that multigravida, specifically multigravida with previous adverse birth outcomes, may be a risk factor to preterm birth (Heaman et al. 2013; Blencowe et al. 2013).

Having a previous low birth weight infant conferred a greater than two-fold risk to have a recurrent low birth weight infant. Recent studies have supported that previous low birth weight is the strongest indicator for subsequent delivery of low birth weight infant (Smid et al. 2017; Shaw, Herbers, and Cutuli 2019). Additionally, previous low birth weight may further exacerbate the risk of other adverse perinatal outcomes including small-for-gestational age (Smid et al. 2017). In a previous study in Karnataka State, India, prior low birthweight was a predictor for preterm birth and low birth weight (Basha, Shivalinga Swamy, and Noor Mohamed 2015). Moreover, poor maternal obstetric characteristics can increase the likelihood of having a low birth weight or preterm birth. In our study, a history of neonatal loss or still birth was also found to be a significant predictor in the unadjusted analysis. Similarly, previous studies have supported that prior maternal obstetric outcomes can influence subsequent birth outcomes (Basha, Shivalinga Swamy, and Noor Mohamed 2015; Shaw, Herbers, and Cutuli 2019). In addition, passive smoking exposure was also determined to be a predictor of low birth weight in the unadjusted analysis. However, these findings were not observed in the multivariate analysis. Prior studies have corroborated that exposure to passive smoking may substantially increase adverse birth outcomes (Xi et al. 2020; Hendryx, Chojenta, and Byles 2020). Moreover, current maternal obstetric characteristics including hypertension (>140/>90 mm Hg) was a significant predictor in preterm birth. Previous studies have confirmed the relationship between hypertension and preterm birth (Wagura et al. 2018; Mulualem, Wondim, and Woretaw 2019). Surprisingly, mild anemia (assessed at the baseline visit) was associated with lower risk of preterm birth. It could be explained that all women received iron supplements after the baseline visit that could explain the unexpected relationship. Therefore, prior and current maternal obstetric history are significant determining factors in predicting adverse birth outcomes.

This study has several limitations worth noting. The data are derived from rural Mysore; therefore, it is difficult to extrapolate the findings to other regions in India since the study results may have limited generalizability. Gestational age was based on last menstrual period, and this may result in some degree of inaccuracy because there were no clinical records to ascertain as the study was done in a rural region. Low birth weight and previous low-birth weight were self-reported, and this may result in inaccurate estimates. Measures such as short interpregnancy intervals were not included in the survey and may be a potential confounder in the analysis. In addition, blood pressure was only assessed once during the baseline visit only so hypertension during pregnancy may not be well-documented. Lastly, self-reported variables including exposure to passive smoking indoors may be subject to social desirability bias due to the nature of the interviewer-administered survey. Nevertheless, to the best of our knowledge, this is the first study that utilizes LCA to examine both preterm birth and low birth weight among pregnant women in rural India. Previous LCA studies have been documented in high resource settings. Further, this study utilized a large sample size from a rural region within India and data was collected prospectively, allowing us to establish the exposure prior to our outcome of interest.

Conclusion

The identification of at-risk women based on multiple characteristics is critical for healthcare providers to tailor interventions for pregnant women to prevent future adverse birth outcomes. The study findings highlighted the importance of utilizing multiple co-occurring risk factors and the impact of compounding risks in determining preterm birth and low birth weight. Low socioeconomic status was determined to be a major predictor for preterm birth and low birth weight. In addition, multigravida women with prior adverse obstetric characteristics influenced birth outcomes. Currently, the Indian government has implemented several funding programs including conditional cash transfers and government subsidies (Rahman and Pallikadavath 2018) to reduce income inequity between individuals of high and low SES. Expansion of these programs are crucial in reducing inequalities and addressing preterm birth and low birth weight in rural India.

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Tables and Figures

Table 1: Description of sociodemographic characteristics of rural pregnant women in Mysore District that were used to determine class membership overall and by class (n=1540)

Characteristics	**Total N=1540 (%)**	**Class 1:** Low SES, Early Marriage, Multigravida, 1 Child or More **n (%)** **710 (46.1%)**	**Class 2:** Low SES, Later Marriage, Primigravida, No Children **n (%)** **354 (23.0%)**	**Class 3:** High SES, Later Marriage, Multigravida, 1 Child or More **n (%)** **214 (13.9%)**	**Class 4:** High SES, Later Marriage, Primigravida, No Children **n (%)** **262 (17.0%)**	**P-value**
	Pregnant Woman's Education					<0.0001**
Primary Education or Less (≤8 years)	603 (39.2%)	406 (57.2%)	176 (49.7%)	21 (9.8%)	0 (0.0%)	
Secondary Education (9-10 years)	629 (40.8%)	268 (37.8%)	178 (50.3%)	92 (43.0%)	91 (34.7%)	
Upper Secondary and Higher (>10 years)	308 (20.0%)	36 (5.1%)	0 (0.0%)	101 (47.2%)	171 (65.3%)	
	Partner's Education					<0.0001**
Primary Education or Less (≤8 years)	817 (53.1%)	493 (69.4%)	246 (69.5%)	15 (7.0%)	63 (24.1%)	
Secondary Education (9-10 years)	478 (31.0%)	183 (25.8%)	89 (25.1%)	97 (45.3%)	109 (41.6%)	
Upper Secondary and Higher (>10 years)	245 (15.9%)	34 (4.8%)	19 (5.4%)	102 (47.7%)	90 (34.4%)	
	Age at Marriage					<0.0001**
Less than 18 years	603 (39.2%)	432 (60.9%)	140 (40.0%)	5 (2.3%)	26 (9.9%)	
18 years and older	937 (60.8%)	278 (39.2%)	214 (60.5%)	209 (97.7%)	236 (90.1%)	

	Primigravida					<0.0001**
No	969 (62.9%)	710 (100.0%)	33 (9.3%)	214 (100.0%)	12 (4.6%)	
Yes	571 (37.1%)	0 (0.0%)	321 (90.7%)	0 (0.0%)	250 (95.4%)	
	Children					<0.0001**
No	723 (47.0%)	66 (9.3%)	354 (0.0%)	41 (19.2%)	262 (100.0%)	
Yes	817 (53.0%)	644 (90.7%)	0 (0.0%)	173 (80.8%)	0 (0.0%)	
	Household Income (In Indian Rupees) (1 USD = 58.9 INR)					<0.0001**
<4000 Indian Rupees	554 (36.0%)	337 (47.5%)	149 (42.1%)	30 (14.0%)	38 (14.5%)	
4000-10,000 Indian Rupees	819 (53.2%)	320 (45.1%)	185 (52.3%)	159 (74.3%)	155 (59.2%)	
>10,000 Indian Rupees	167 (10.8%)	53 (7.5%)	20 (5.7%)	25 (11.7%)	69 (26.3%)	

Table 2: Description of maternal obstetric covariates among rural pregnant women in Mysore District overall and by class membership (n=1540)

Characteristics	Total n=1540 (%)	**Class 1:** Low SES, Early Marriage, Multigravida, 1 Child or More **n (%) 710 (46.1%)**	**Class 2:** Low SES, Later Marriage, Primigravida, No Children **n (%) 354 (23.0%)**	**Class 3:** High SES, Later Marriage, Multigravida, 1 Child or More **n (%) 214 (13.9%)**	**Class 4:** High SES, Later Marriage, Primigravida, No Children **n (%) 262 (17.0%)**	P-value
	Age Categories					<0.0001**
<20 years	361 (23.4%)	107 (15.1%)	172 (48.6%)	3 (1.4%)	79 (30.2%)	
20-24 years	983 (63.8%)	503 (70.9%)	149 (42.1%)	167 (78.0%)	164 (62.6%)	
≥ 25 years	196 (12.7%)	100 (14.1%)	33 (9.3%)	44 (20.6%)	19 (7.3%)	
	Delivery Location					0.0173*
Home	12 (0.8%)	9 (1.3%)	0 (0.0%)	3 (1.4%)	0 (0.0%)	
Sub-center/ Primary Health Center/District Health	794 (51.8%)	362 (51.5%)	204 (57.6%)	101 (47.2%)	127 (48.5%)	
Maternity Hospital/Private Nursing Home	727 (47.4%)	332 (47.2%)	150 (42.4%)	110 (51.4%)	135 (51.5%)	
	Baseline Sexually Transmitted Infection					0.5997
No	1408 (92.7%)	655 (93.2%)	314 (91.0%)	197 (93.4%)	242 (93.1%)	
Yes	111 (7.3%)	48 (6.8%)	31 (9.0%)	14 (6.6%)	18 (6.9%)	

	Previous Stillbirth or Neonatal Loss					0.0157*
No	1479 (96.0%)	673 (95.0%)	344 (97.2%)	203 (94.9%)	259 (98.9%)	
Yes	61 (4.0%)	37 (5.2%)	10 (2.8%)	11 (5.1%)	3 (1.2%)	
	History of Spontaneous Abortion					<0.0001**
No	1387 (90.1%)	614 (86.5%)	339 (95.8%)	178 (83.2%)	256 (97.7%)	
Yes	153 (9.9%)	96 (13.5%)	15 (4.2%)	36 (16.8%)	6 (2.3%)	
	History of Induced Abortion					<0.0001**
No	1491 (96.8%)	684 (96.3%)	353 (99.7%)	193 (90.2%)	261 (99.6%)	
Yes	49 (3.2%)	26 (3.7%)	1 (0.3%)	21 (9.8%)	1 (0.4%)	
	Passive Smoking					<0.0001**
No	1260 (81.8%)	553 (77.9%)	282 (79.7%)	191 (89.3%)	234 (89.3%)	
Yes	280 (18.2%)	157 (22.1%)	72 (20.3%)	23 (10.8%)	28 (10.7%)	
	Previous Low Birth Weight					<0.0001**
No	1258 (81.7%)	524 (73.8%)	332 (93.8%)	151 (70.6%)	251 (95.8%)	
Yes	282 (18.3%)	186 (26.2%)	22 (6.2%)	63 (29.4%)	11 (4.2%)	
	Baseline Anemia Status					0.5873
Normal (>11 g/dl)	373(24.2%)	168 (23.4%)	83 (23.5%)	61 (28.5%)	61 (23.3%)	
Mild (10.0-10.9 g/dl)	312 (20.3%)	136 (43.6%)	78 (22.0%)	39 (18.2%)	59 (22.5%)	
Moderate/Severe (≤ 9.9 g/dl)	855 (55.6%)	406 (57.2%)	193 (54.5%)	114 (53.2%)	142 (54.2%)	

	History of Hypertension					0.0007**
No	1512 (98.2%)	691 (97.3%)	353 (99.7%)	206 (96.3%)	262 (100.0%)	
Yes	28 (1.8%)	19 (2.7%)	1 (0.3%)	8 (3.7%)	0 (0.0%)	
	Baseline Hypertension Categories					0.2329
Normal (<120/80 mm Hg)	919 (59.7%)	427 (60.1%)	217 (61.3%)	124 (57.9%)	151 (57.6%)	
Pre-hypertension (120-139 mm Hg/ 0r 80-89 mm Hg)	579 (37.6%)	265 (37.3%)	133 (37.6%)	80 (37.4%)	101 (38.6%)	
Hypertension (>140/>90 mm/Hg)	42 (2.7%)	18 (2.5%)	4 (1.1%)	10 (4.7%)	10 (3.8%)	

Table 3: Crude Odds Ratio and Adjusted Odds Ratio of Preterm Birth and Low Birth Weight by characteristics of rural pregnant women in Mysore District obtained from binary logistic regression

Characteristics	PTB Crude OR (95% CI)	PTB Adjusted OR (95% CI)	LBW Crude OR (95% CI)	LBW Adjusted OR (95% CI)
Class				
Class 1 vs. Class 4	**1.79 (1.10-2.91)***	**1.77 (1.05-2.97)***	**1.75 (1.08-2.84)***	1.35 (0.81-2.25)
Class 2 vs. Class 4	1.35 (0.78-2.34)	1.35 (0.77-2.43)	**2.83 (1.71-4.71)***	**2.50 (1.49-4.21)***
Class 3 vs. Class 4	1.51 (0.83-2.75)	1.68 (0.88-3.21)	1.13 (0.60-2.12)	0.92 (0.48-1.80)
Age (categorical variable)				
<20 years vs. ≥ 25 years	0.90 (0.63-1.29)	**2.00 (1.08-3.71)***	0.79 (0.56-1.10)	0.95 (0.56-1.60)
20-24 years vs. ≥ 25 years	0.61 (0.32-1.13)	1.49 (0.87-2.57)	0.91 (0.54-1.52)	0.92 (0.58-1.45)
Delivery Location				
Home vs. Maternity Hospital/Private Hospital	2.66 (0.71-10.02)	2.09 (0.54-8.19)	1.45 (0.31-6.74)	1.62 (0.34-7.80)
Sub-center/ Primary Health Center/District Health vs. Maternity Hospital/Private Hospital	1.18 (0.86-1.60)	1.11 (0.81-1.53)	1.31 (0.97-1.75)	1.29 (0.95-1.75)
Baseline Sexually Transmitted Infection				
Yes vs. No	1.36 (0.79-2.34)	1.35 (0.78-2.35)	1.41 (0.85-2.34)	1.42 (0.84-2.40)
History of Neonatal Loss or Still Birth				
Yes vs. No	1.27 (0.61-2.61)	1.15 (0.54-2.42)	**1.92 (1.04-3.54)***	1.58 (0.83-3.04)
History of Spontaneous Abortion				
Yes vs. No	1.40 (0.88-2.23)	1.02 (0.58-1.80)	1.31 (0.84-2.06)	0.94 (0.55-1.61)
History of Induced Abortion				
Yes vs. No	0.64 (0.23-1.78)	0.49 (0.17-1.43)	0.70 (0.28-1.79)	0.60 (0.22-1.60)
Passive Smoking				
Yes vs. No	1.08 (0.73-1.60)	1.06 (0.70-1.60)	**1.46 (1.03-2.07)***	1.41 (0.98-2.03)
Previous Low Birth Weight				

Yes vs. No	**1.60 (1.12-2.29)***	1.42 (0.90-2.22)	**1.74 (1.24-2.43)***	**2.15 (1.40-3.29)***
Anemia				
Mild vs. Normal	0.59 (0.35-1.00)	**0.58 (0.33-0.98)***	0.97 (0.64-1.47)	0.93 (0.61-1.43)
Moderate/Severe vs. Normal	1.13 (0.78-1.62)	1.12 (0.77-1.63)	0.75 (0.53-1.06)	0.71 (0.50-1.01)
History of Hypertension				
Yes vs. No	1.59 (0.60-4.23)	1.19 (0.43-3.29)	1.04 (0.36-3.03)	0.98 (0.33-2.96)
Hypertension				
Pre-hypertension (120-139 mm Hg/ 0r 80-89 mm Hg) vs. Normal	1.18 (0.86-1.62)	1.22 (0.88-1.70)	1.01 (0.75-1.36)	0.96 (0.71-1.32)
Hypertension (>140/>90 mm/Hg) vs. Normal	**2.16 (1.01-4.64)***	**2.28 (1.02-5.07)***	0.65 (0.23-1.85)	0.67 (0.23-1.96)

MANUSCRIPT 2

Evaluating the moderating role of Accredited Social Health Activists (ASHA) home visits and ASHA-accompanied ANC visits on preterm birth and low birth weight in rural Mysore District, India

Abstract

Background

The Indian government established the Accredited Social Health Activists (ASHA) program in 2006 to improve access and healthcare coverage in rural regions. The objective of this study was to examine the moderating role of ASHA home visits and ASHA-accompanied antenatal care visits (ANC) on the relationship between sociodemographic latent classes of pregnant women and preterm birth and low birth weight infants in rural Mysore District, India.

Methods

Utilizing a prospective cohort study conducted between 2011–2014, secondary data analysis was performed among 1540 pregnant women in rural Mysore, India. Latent Class Analysis was performed to identify sociodemographic distinct patterns. Multivariable logistic regression was performed to examine the moderating effects of ASHA-accompanied ANC visits and ASHA home visits on preterm birth and low birth weight.

Results

Among women who never/rarely had ASHA-accompanied ANC visits, women in Class 1 "low socioeconomic status (SES)/early marriage/multigravida/1 child or more" and Class 3 "high SES/later marriage/multigravida/1 child or more" had higher odds of preterm birth (adjusted odds ratio [aOR]: 2.62, 95% Confidence Interval [CI]: 1.12–6.12; aOR: 3.47 95% CI:1.31–9.15, respectively) compared to Class 4 "high SES/later marriage/primigravida/no children." Among women who rarely or never had ASHA-accompanied ANC visits, women in Class 2 "low SES/later marriage/primigravida/no children" had higher odds of low-birth-weight infants.

Conclusion

The findings demonstrate that ASHA accompanying women to ANC moderates the risk of preterm births among women in high-risk SES groups. Targeted policies and interventions in improving and strengthening the ASHA program to reduce inequities in adverse birth outcomes in rural India.

Introduction

Despite significant strides in advancing maternal and neonatal health, pregnancy and childbirth remains a high risk and vulnerable period. Each year, nearly 2.4 million babies die within the first month of life, and approximately 300,000 women die due to pregnancy and child-birth related complications globally (Liu et al. 2016; World Health Organization 2020). The majority of these deaths are preventable through implementation of interventions along the continuum of care, that is, before conception, prenatal and postnatal care (Bhutta et al. 2014; Kuhnt and Vollmer 2017). India has consistently ranked as the country with the highest number of newborn deaths in the past decade

(UNICEF 2020). Between 1990 and 2016, the neonatal mortality rates (NMR) in India from preterm birth and low birth weight infants increased from 12.3 per 1000 live births to 13.3 per 1000 live births, predominantly in poorer states and rural regions (Fadel et al. 2017). In the early 2000s, the National Family Health Survey (NFHS-2) (International Institute of Population Health Sciences 2016) reported a higher NMR in rural India compared to urban India (46.7 per 1000 live births vs. 31.7 per 1000 live births), and the most recent data indicates that this rural-urban disparity has persisted over time (International Institute of Population Health Sciences 2016). These disparities have been attributed to low socioeconomic status, lack of access to antenatal care (ANC) services, restricted geographical mobility to healthcare institutions, and reduced quality of care (Saikia et al. 2013).

Due to the existing geographical inequities, the Indian government established the National Rural Health Mission (NRHM) in 2005 to strengthen the healthcare system by increasing institutional delivery access and ANC services coverage among the poorest populations (National Health Mission 2020). A major component of the NRHM program is the Accredited Social Health Activist (ASHA) program, which was launched in 2006 (National Health Mission 2020). The program consists of ASHAs, all-female cadre of frontline health workers who serve as vital intermediaries between the community and the public health system to improve access and healthcare coverage in rural regions (National Health Mission 2020). The key roles include counseling and educating pregnant women, supporting healthcare service delivery by conducting home visits, registering women for ANC visits, offering nutritional support, and providing ancillary services such as transportation for institutional delivery (National Health Mission 2020).

Even though ASHAs are voluntary workers, they are often rewarded through performance-based incentives by the government for facilitating the utilization of reproductive health services by pregnant women.

Antenatal care services have been specifically recommended by the World Health Organization (WHO) for monitoring, screening, educating, preventing, and treating any pregnancy complications (World Health Organization 2016). Timely and appropriate ANC visits are vital in reducing adverse birth outcomes. However, several barriers in accessing ANC services in rural India have been well-documented including low socioeconomic status, limited access to healthcare, restricted geographical mobility, and limited awareness of ANC (Munuswamy et al. 2013). A recent national survey indicated that women residing in urban India were more likely to receive the recommended ANC visits compared to those residing in rural areas (66% vs. 45%) (International Institute of Population Health Sciences 2016). Research has shown that ASHAs have been instrumental in increasing ANC visits among marginalized and poor women in rural settings (Agarwal et al. 2019; Lyngdoh et al. 2018). Therefore, ASHAs play an important role in promoting uptake of ANC services among pregnant women in rural India. Since the launch of the program in 2006, nearly one million ASHAs have been trained and deployed throughout India, and it remains one of the largest community health workers program worldwide (Scott, George, and Ved 2019a).

Given the massive expansion of ASHA programs throughout India, it is critical to perform assessments to examine the programs' effectiveness on health outcomes. Previous studies have examined performance assessments on ASHA programs and maternal utilization of health services (Agarwal et al. 2019; Paul and Pandey 2020;

Fathima et al. 2015) while less is known about the impact of the ASHAs on birth outcomes. A recent randomized clinical trial in India revealed that ASHA-supported women groups were associated with decreased neonatal mortality (Tripathy et al. 2016).

Recent studies have documented that preterm birth and low birth weight infants are attributed to multiple co-occurring risk factors compared to single risk factors examined in multivariate analysis (Shaw, Herbers, and Cutuli 2019; Hendryx, Chojenta, and Byles 2020). Therefore, complex methodological approaches such as latent class analysis have been increasingly adopted to identify high-risk groups of pregnant women. To our knowledge, no studies have utilized person-centered approaches in evaluating the relationship between ASHA visits during pregnancy and birth outcomes i.e., preterm birth and low birthweight in rural India. Therefore, our study sought to examine the moderating role of ASHA home visits and ASHA-accompanied ANC visits on the relationship between sociodemographic latent classes of pregnant women and preterm birth and low birth weight infants in rural Mysore District, India.

Materials and Methods

Study Population and Design

We utilized data from the Saving Children Improving Lives (SCIL) project. This was a prospective cohort study conducted between 2011 and 2014 among rural pregnant women from Mysore district in Karnataka State in Southern India. Approximately 58.5% of Mysore population reside in rural areas, where nearly half of the 3 million people are women ('Mysore District : Census 2011 data' Census 2011). The original SCIL research objective was to examine the feasibility of integrated antenatal care and HIV testing among pregnant women. This was achieved through several initiatives including community education, mobile medical clinics and social mobilization through women self-help groups. For additional details on the study, the protocol was previously published in Kojima et al (Kojima et al. 2017). The institutional review boards of the authors institutes approved this study.

Pregnant women living in Mysore district received integrated ANC and HIV testing through the mobile medical clinics. During the visit, the pregnant women were informed of the study. The eligibility criteria for the study included pregnant women who resided in the Mysore district for more than 6 months. Subsequently, these women who met these criteria enrolled in the study. Voluntary written informed consent in the local language of *Kannada* was obtained from eligible women. The PHRII staff who are trained interviewers in *Kannada*, administered a baseline questionnaire on sociodemographic, medical, and reproductive history. Clinical laboratory examinations on urine, blood and vaginal samples were collected by trained PHRII clinical workers as a part of the antenatal care to screen for sexually transmitted infections including syphilis, hepatitis B, HIV, and bacterial vaginosis. The laboratory testing was performed in the PHRII lab after data collection. All women enrolled in the study were followed within 15 days of delivery, and 6 and 12 months after delivery. Data on predictors were collected during the baseline questionnaire during the antenatal period, and data on outcomes were collected during the first follow-up of the study, which was within 15 days of delivery in the postnatal period. To be included in our analysis, we only selected women aged 18 years and older and excluded 8% of the sample due to missing data on last menstrual period or missing dates on deliveries (n=40) and infant deaths (n=98). Therefore, the total study sample utilized in the analysis was 1,540.

Study Measures

Outcomes

The outcomes in the study were preterm birth and low birth weight infants. Preterm birth was defined as live births born before 37 weeks according to the last menstrual period (World Health Organization 2018a). Low birth weight infant was defined according to the WHO as an infant born weighing less than 2,500 grams (World Health Organization 2004).

Predictor variables

The predictors in our study were latent classes determined through the PROC LCA method using SAS/STAT v14.2 software. A total of six sociodemographic variables (pregnant women's education, partner education, total household income, age at marriage, primigravida status, and number of children) were selected based on latent class analysis (LCA) to classify women into distinct sociodemographic patterns. The analytical approach included conducting a model comparison approach through testing unconditional models without covariates in the LCA. Subsequently, the model fit was tested using 2 through 6 latent classes. The appropriate selection of latent classes was based on Bayesian Information Criterion (BIC), Adjusted Bayesian Information Criterion (aBIC) and Adjusted Information Criterion (AIC), entropy values, and the interpretability of latent classes (Nylund-Gibson and Choi 2018). Based on the model fit parameters, the model with four latent classes was selected as the best fitting and most parsimonious model with lowest BIC (445.41), adjusted BIC (321.52), and AIC (237.17) and distinct class separation based on an entropy value of 0.75. The four classes classified as: "low socioeconomic (SES)/early marriage/multigravida/1 child or more", "low SES/later marriage/primigravida/no children", "high SES/later marriage/multigravida/1 child or more," and "high SES/later marriage/primigravida/no children" were labeled as Class 1–Class 4, respectively.

Moderators

The moderator variables were: ASHA home visits during pregnancy and ASHA-accompanied ANC visits during pregnancy. ASHA home visits refer to ASHA workers visiting and counseling pregnant women at home during and after pregnancy, recommending antenatal checkups, creating a birth-preparedness checklist, informing safe delivery practices and offering institutional delivery support (National Health Mission 2020). ASHA-accompanied ANC visits refers to ASHA workers escorting pregnant women to attend ANC visits in medical clinics (National Health Mission 2020). The frequency of ASHA exposure was originally labeled as never, rarely (once in 3 months), occasionally (every two months), and regularly (once a month). Due to limitations associated with sample size in the analysis, the ASHA home visits and ASHA-accompanied ANC visits were categorized as a dichotomous indicator: "never/rarely" and "occasionally/regularly".

Covariates

The covariates in the study were selected based on prior literature review on maternal obstetric factors (Blencowe et al. 2013). The participant's age was categorized as (<20 years, 20-24 years, and ≥ 25 years). Delivery location was categorized as home, public health institution (sub-center/district health/primary health center), and private health institution (maternity hospital/private nursing home). Self-reported measures for maternal obstetric characteristics included previous still birth or neonatal loss (yes or no), history of spontaneous abortion (yes or no), history of induced abortion (yes or no), exposure to passive smoking indoors (yes or no), previous low birth weight infants (yes or no), and frequency of ANC visits (<8 ANC visits and ≥ 8 ANC visits). Baseline sexually transmitted infections (STI) (yes or no) was defined as either having hepatitis B or HIV or bacterial vaginosis.

The presence of chronic diseases was self-reported and included history of hypertension classified as yes or no. Baseline anemia and hypertension were based on physical examination and laboratory results. Anemia was assessed by hemoglobin levels categorized as normal for hemoglobin levels of 11.0g/dl or higher, mild for 10-10.9 g/dl, and moderate/severe as ≤10 g/dl respectively(World Health Organization 2011b). Hypertension categories were based on measured blood pressure levels as follows: normal (<120/80 mm Hg), pre-hypertension (120–139 mm Hg systolic or 80–89 mm Hg diastolic) and hypertensive categories (≥140 mm Hg systolic or ≥90 mm Hg diastolic) (Barbara 2006).

Statistical Analysis

Descriptive statistics were performed to examine the characteristics of the latent classes. Subsequently, univariate analyses were conducted by applying chi-square tests to examine the relationship of the latent classes with the covariates, ASHA home visits, and ASHA-accompanied ANC visits. Unadjusted logistic regression was conducted to examine the association between the latent classes and preterm birth and low birth weight infant (Model 1). In model 2, multivariable logistic regression was conducted to examine the association between the latent classes and preterm birth and low birth weight after adjusting for the covariates.

Subsequently, we performed a moderation analysis of the recommended ASHA components separately to determine their differential effect on the relationship between latent classes and preterm birth and low birth weight infant status. Model 3 included the main effects of the latent classes, ASHA home visits, and the interaction between the two after adjusting for covariates. Model 4 included the main effects of the latent classes, ASHA-accompanied ANC visits, and the interaction between the two after adjusting for covariates. The level of interactions was computed using the LSMEANS, LSMESTIMATE, and SLICE functions within SAS/STATv14.2 PROC LOGISTIC. Associations were considered significant at the alpha level of 0.05.

Results

Sample Characteristics

Table 1 displays the sociodemographic patterns of the pregnant women based on the LCA approach. Approximately 40% of the participants and more than half (53%) of their partners had received no more than a primary education. Almost 40% of the women married before they were 18 years of age. More than a third of the women were primigravida, and 53% of women had children. Only 10.8% earned a total monthly household income of 10,000 or more Indian rupees (INR) (approximately USD $170 with 1 USD = 58.9 INR during the data collection period). Table 2 shows univariate analysis of ASHA home visits and ASHA-accompanied ANC visits during pregnancy by the latent classes and the covariates. Approximately 17% of the women reported never/rarely having an ASHA home visit during their pregnancy, while nearly 40% of the women reported never/rarely having ASHA-accompanied ANC visits. Of those who had never/rarely received ASHA home visits during pregnancy, a higher proportion of those participants belonged to Class 1 “low socioeconomic (SES)/early Marriage/Multigravida/1 Child or More”, were older than 20 years of age, delivered in a public/private institution, had a previous stillbirth or neonatal loss, had a history of spontaneous abortion, had mild, moderate, and severe anemia levels, and had baseline pre-hypertension and hypertension. Of those who never/rarely received ASHA-accompanied ANC visits, a higher proportion belonged to Class 1, were older than 20 years of age, delivered in a public/private institution, had a baseline STI, had a history of spontaneous abortion, had a previous low birth weight, had baseline pre-hypertension and hypertension, and attended <8 ANC visits.

Multivariable Logistic Regression

Preterm Birth

Table 3 reports the unadjusted odds ratio (OR), adjusted odds ratio (aOR), and 95% confidence intervals (CI) for the association between latent classes and preterm birth. After adjusting for covariates, no significant associations were observed in the relationship between latent classes and preterm birth in models 1, 2 or 3. However, in model 4 which includes the interaction between ASHA-accompanied ANC visits and latent classes, women in Class 1 “low SES/early marriage/multigravida/1 child or more” had higher odds of preterm birth (aOR: 1.83, 95% CI:1.06–3.14) as compared with women in Class 4 “high SES/later marriage/primigravida/no children.” In the unadjusted model, the odds of preterm birth were significantly higher among women who never/rarely had ASHA-accompanied ANC visits when compared with those who occasionally/regularly had ASHA-accompanied ANC visits (OR 1.58: 95% CI: 1.09–2.09). However, this association did not remain significant after adjusting for covariates.

No significant interaction was observed in the relationship between latent classes and ASHA-accompanied ANC visits on preterm birth. However, significant differences were observed between the classes—among women who never/rarely had ASHA-accompanied ANC visits: women in Class 1, and Class 3 had higher odds of preterm birth compared to Class 4 (aOR: 2.62, 95% CI: 1.12–6.12 and aOR: 3.47, 95% CI: 1.31–9.15 respectively). Among women who never/rarely had ASHA-accompanied ANC visits, women in Class 2 "low SES/later marriage/primigravida/no children" had a two-fold higher odds of preterm births (aOR: 2.07, 95% CI: 0.83–5.17) as compared to Class 4; however this was not statistically significant. In contrast, among women who occasionally/regularly had ASHA-accompanied ANC visits, no significant associations were observed among the classes on preterm birth. Additionally, the aORs computed in this group were around 1.00, which were much lower compared to those women who never or rarely had ASHA-accompanied ANC visits. No significant interactions were observed in the relationship between latent classes and ASHA home visits on preterm birth.

Low Birth Weight

Table 4 displays the association between latent classes and low birth weight. After adjusting for covariates, women in Class 2 compared with Class 4 reported higher odds of low birth weight infants in models 1 through 4. No significant interaction was observed in the relationship between latent classes and ASHA-accompanied ANC visits on delivery of low birth weight infants. For both ASHA-accompanied ANC visit strata, women in Class 2 had higher odds of low birth weight infant aOR: 2.26, 95% CI:1.10–4.63 for never/rarely had ASHA accompanied ANC visits and aOR: 2.70, 95% CI:1.27–

5.74 for women who occasionally/regularly had ASHA accompanied ANC visits) compared to women in Class 4.

No significant interactions were observed between the latent classes and ASHA home visits on delivery of low birth weight infants. However, among women who occasionally/regularly had ASHA home visits, those in Class 2 had higher odds of having a low birth weight infant (aOR: 2.24, 1.29–3.92) compared with those in Class 4. Moreover, higher odds of low birth weight are displayed in all classes among women who never/rarely had ASHA home visits compared to women who occasionally/regularly had ASHA home visits.

Discussion

Our study findings suggest that among women who never/rarely had ASHA-accompanied visits, those in high-risk SES classes had higher odds of adverse birth outcomes compared with women in lower risk SES classes. ASHA home visits did not moderate the association between SES classes and preterm birth or delivery of low birth weight infant. Most notably, Class 1 “low SES/early marriage/multigravida/1 child or more” was associated with preterm birth, while Class 2 “low SES/later marriage/primigravida/no children” was associated with low birth weight infant; both were high-risk SES classes.

Although preterm birth and low birth weight are inextricably linked, the findings of the study demonstrated that distinct risk profiles influence these outcomes differently. Women in Class 1, comprising nearly half of the participants, were characterized by the interplay of risk factors including low SES, early marriage, multigravida, 1 child or more, which have been documented to have higher likelihood of adverse birth outcomes

(Blumenshine et al. 2010; Simkhada et al. 2008). Further, women in Class 2 characterized by co-occurring low SES, later marriage, primigravida and no children were more likely to deliver a low birth weight infant. It has also been posited that the effect of maternal-fetal competition for nutrients among first-time young pregnant women as a risk factor for delivery of. low birth weight infant (Mukhopadhyay, Chaudhuri, and Paul 2010). Moreover, they may have underlying conditions and lack access to antenatal care that may further exacerbate low birth weight. Overall, these two high-risk classes share a common risk factor, low SES. A systematic review conducted by Blumenshine and colleagues reported that socioeconomic disadvantage is the primary risk factor for adverse birth outcomes (Blumenshine et al. 2010).

The current study identified the importance of ASHA accompanying women to their ANC visits in moderating the relationship between high-risk classes and preterm birth. Our findings found that among women who never or rarely had ASHA-accompanied ANC visits, women in Class 1 were more likely to have a preterm delivery. The association between co-occurring risk factors including low SES, early marriage, and higher parity and preterm birth has been well-established in prior studies (Blumenshine et al. 2010; Simkhada et al. 2008). Further, women with previous pregnancy experience may be less inclined to seek antenatal care services and may have opted out of receiving ASHA services (Blencowe et al. 2013; Scott, George, and Ved 2019a). Despite all the disadvantages in Class 1, an ASHA can help overcome those barriers to accessing care, ultimately leading to healthy birth outcomes. Exposure to ASHAs in marginalized and rural communities has demonstrated effectiveness in expanding ANC service coverage, increasing institutional deliveries, increasing access to conditional cash transfers, improving immunization rates, decreasing antenatal anxiety in pregnant women, and reducing perinatal deaths (Agarwal et al. 2019; Wagner et al. 2018; Bhushan et al. 2020; Paul and Pandey 2020; Tripathy et al. 2016; Kiplagat et al. 2020). They act as vital support system to encourage and mobilize rural women to engage with healthcare providers during pregnancies.

Surprisingly, among women who never or rarely had ASHA-accompanied ANC visits, women in Class 3 had higher odds of preterm birth compared to Class 4. Women in Class 3 were characterized by a distinct profile of high SES, later marriage, multigravida and 1 child or more. A recent study established that there were no differential effects of ASHA visits based on sociodemographic status (Seth et al. 2017). Moreover, the high SES group within this rural community was not wealthy, and it is not comparable to high SES in an Indian urban community or well-resourced setting. Regardless of their socioeconomic status, previous studies shows that women who reside in rural areas have poorer birth outcomes due to lack of equitable access to quality healthcare (Dongarwar and Salihu 2020; Amjad et al. 2019). Additionally, the findings highlight that, nearly half of the women who never/rarely had ASHA-accompanied ANC visits had attended fewer than eight ANC visits which may explain the higher odds of poor birth outcomes. The WHO recommended optimizing systematic low-cost interventions such as antenatal care, community health worker initiatives such as ASHA support in all rural settings that will greatly improve maternal and child health outcomes (World Health Organization 2016).

In addition, our study findings revealed that among women who rarely or never had ASHA-accompanied ANC visits, women in Class 2 had higher odds of low birth weight infants. Similar observations were also reported among women who occasionally or regularly had ASHA-accompanied ANC visits. While these findings may seem surprising, women in Class 2 were associated with having low birth weight infants across all four models, and may be a group of women with barriers that were not addressed by ASHAs in this study. Women who are low SES and pregnant for the first time may also lack the appropriate resources and knowledge in seeking reproductive health services. Thus, community health workers, like ASHAs, are vital intermediaries in the mobilizing and facilitating ANC services for primigravida women (Okuga et al. 2015). Prior studies have shown that primigravida women who tend to seek antenatal care services have healthy birth outcomes (Tuladhar and Dhakal 2011). Several community health worker programs that have targeted women have observed increased ANC visits, increased institutional deliveries, and healthy birth outcomes (Agarwal et al. 2019; Tripathy et al. 2016). However, none of the studies has solely focused on primigravida women, particularly younger women from low-resource settings. Therefore, our findings underscore the need for a targeted outreach by ASHAs geared towards first-time rural mothers to promote healthy birth outcomes.

While the NRHM recommends ASHA home visits as essential services during pregnancy, our study did not find a significant moderating effect of ASHA home visits on the relationship between the latent SES classes and preterm birth. This may be partly explained by the lack of clear guidelines for the minimum number of required home visits and services offered during the ASHA home visits outlined in the policy document (National Health Mission 2020). Despite the ASHA program being standardized throughout all states, ASHA training varies depending on the state and the resources available, which could further lead to heterogeneity and inconsistencies of service delivery. A recent systematic review reported that ASHAs negative performance may have been attributed to several inadequacies including, knowledge gaps, limited ASHA training and supervision, challenges with referral, dissatisfaction related to pay, limited coverage, and sub-optimal performance of ASHAs (Scott, George, and Ved 2019a). It is crucial for the NRHM to incorporate strategies to recruit, educate, train, and retain ASHAs to improve healthcare access, quality care and coverage for marginalized and rural pregnant women. Moreover, the government should set up a standard checklist for each visit to ensure standardization throughout the states to promote equitable outcomes. We also found that ASHA home visits had no apparent benefit for women in Class 2. This could be because women in Class 2 were already at a higher risk of low birth weight as shown in all models and hence ASHA home visits were ineffective. It is worth mentioning that while we observed non-significant results, women who never/rarely had ASHA home visits in higher risk SES classes tended to have higher odds of low birth weight infants and preterm birth compared with those who occasionally/regularly had ASHA visits across the same classes. The non-significant results may also be due to reduced statistical power from smaller sample represented in these groups.

Consistent with previous findings, age and previous low birth weight were risk factors for preterm birth and subsequent low birth weight infants respectively (Blencowe et al. 2013). The adjusted analysis did not show significant association of the frequency of ANC visits and preterm birth, this may be as a result of controlling for a number of SES covariates. However, the unadjusted findings indicated that women who had fewer than eight ANC visits during their pregnancy were significantly more likely to have a preterm delivery. The WHO recently updated its ANC guidelines to a minimum of eight ANC visits as compelling evidence suggested that this can reduce perinatal deaths by up to eight per 1000 live births compared to the prior recommendation of four ANC visits (World Health Organization 2016). Therefore, this affirms the important role of updating the Indian antenatal care guidelines to align with the recent WHO recommendation of a minimum of eight ANC visits to promote healthy birth outcomes (World Health Organization 2016).

Some limitations were observed in our study. Preterm birth was defined by the gestational age based on the last menstrual period, and there may be degrees of inaccuracy due to the lack of ultrasound assessments to ascertain these measures. Specific measures such as hemoglobin and blood pressure were only assessed during the enrollment of the study in the second trimester, and not throughout the pregnancy. Some measures including short inter-pregnancy intervals and the timeliness for the ANC visits were not included in the survey and may serve as residual confounders. The survey questionnaire did not include any assessments done during ASHA home visits and ASHA-accompanied ANC visits to assess the differences observed in our study. However, a distinction between the two is that with ASHA-accompanied ANC visits, pregnant women receive assistance in navigating the medical care system facilitating the identification of pregnancy complications; this assistance with medical care navigation is lacking during home visits (National Health Mission 2020). In addition, the three-week training for ASHA workers is inadequate, with ASHA workers performing home visits mainly offer counseling, recommend ANC visits, and facilitate institutional deliveries but do not provide clinical care during home visits (Press Information Bureau Government of

India Ministry of Health and Family Welfare 2015). Hence, this may explain why ASHA-accompanied ANC visits were more effective. The data are from rural Mysore District in Karnataka State, India, and may have limited generalizability throughout India. However, it is worth noting that ASHA is a national program that is implemented across all the states, so the study recommendations may apply to all states in the country.

Nevertheless, there were several strengths in our study. This study is a prospective cohort study with a rich dataset to assess the measure of temporality between exposure and outcomes of interest. This study is one of the few studies that has utilized latent class analysis to examine the co-occurrence of risk factors among pregnant women in low-resource settings. Specifically, this analysis offers a robust analytical approach to examine sociodemographic class patterns that may not be accounted by traditional multivariable regression analyses. Lastly, this study examined the moderating role of ASHA home visits and ASHA-accompanied ANC visits during pregnancy which has not been previously studied.

Conclusion

ASHA services are truly essential among rural women in India to increase antenatal care to prevent adverse birth outcomes and promote successful and thriving healthy pregnancies. The findings demonstrate that ASHA accompanying pregnant women to ANC moderates the risk of preterm births among women in high-risk SES groups. No significant interaction was observed in the relationship of ASHA home visits on preterm birth and low birth weight in high-risk groups. A comprehensive program evaluation is needed to quantify the impact of the ASHA program, identify its strengths and weaknesses, to improve the program and thus, ultimately reduce inequities in preterm birth and low birth weight in rural India.

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Tables and Figures

Table 1: Description of sociodemographic characteristics of rural pregnant women in Mysore District that were used to determine class membership overall and by class (n=1540)

Characteristics	Total N=1540 (%)	Class 1: Low SES, Early Marriage, Multigravida, 1 Child or More n (%) 710 (46.1%)	Class 2: Low SES, Later Marriage, Primigravida, No Children n (%) 354 (23.0%)	Class 3: High SES, Later Marriage, Multigravida, 1 Child or More n (%) 214 (13.9%)	Class 4: High SES, Later Marriage, Primigravida, No Children n (%) 262 (17.0%)	P-value
	Pregnant Woman's Education					<0.0001**
Primary Education or Less (≤8 years)	603 (39.2%)	406 (57.2%)	176 (49.7%)	21 (9.8%)	0 (0.0%)	
Secondary Education (9-10 years)	629 (40.8%)	268 (37.8%)	178 (50.3%)	92 (43.0%)	91 (34.7%)	
Upper Secondary and Higher (>10 years)	308 (20.0%)	36 (5.1%)	0 (0.0%)	101 (47.2%)	171 (65.3%)	
	Partner's Education					<0.0001**
Primary Education or Less (≤8 years)	817 (53.1%)	493 (69.4%)	246 (69.5%)	15 (7.0%)	63 (24.1%)	
Secondary Education (9-10 years)	478 (31.0%)	183 (25.8%)	89 (25.1%)	97 (45.3%)	109 (41.6%)	
Upper Secondary and Higher (>10 years)	245 (15.9%)	34 (4.8%)	19 (5.4%)	102 (47.7%)	90 (34.4%)	
	Age at Marriage					<0.0001**
<18 years	603 (39.2%)	432 (60.9%)	140 (40.0%)	5 (2.3%)	26 (9.9%)	
≥ 18 years	937 (60.8%)	278 (39.2%)	214 (60.5%)	209 (97.7%)	236 (90.1%)	
	Primigravida					<0.0001**
No	969 (62.9%)	710 (100.0%)	33 (9.3%)	214 (100.0%)	12 (4.6%)	

Yes	571 (37.1%)	0 (0.0%)	321 (90.7%)	0 (0.0%)	250 (95.4%)	
	Children					<0.0001**
No	723 (47.0%)	66 (9.3%)	354 (0.0%)	41 (19.2%)	262 (100.0%)	
Yes	817 (53.0%)	644 (90.7%)	0 (0.0%)	173 (80.8%)	0 (0.0%)	
	Monthly Household Income (In Indian Rupees) (1 USD = 58.9 INR)					<0.0001**
<4000 Indian Rupees	554 (36.0%)	337 (47.5%)	149 (42.1%)	30 (14.0%)	38 (14.5%)	
4000-10,000 Indian Rupees	819 (53.2%)	320 (45.1%)	185 (52.3%)	159 (74.3%)	155 (59.2%)	
>10,000 Indian Rupees	167 (10.8%)	53 (7.5%)	20 (5.7%)	25 (11.7%)	69 (26.3%)	

Table 2: Description of maternal obstetric covariates among rural pregnant women in Mysore District by ASHA home visits and ASHA-accompanied ANC visits n=1540)

Characteristics	ASHA home visits Never/Rarely n=258 (16.9%)	ASHA home visits Occasionally/ Regularly n=1273 (83.2%)	P-value	ASHA ANC visits Never/Rarely n=612 (39.7%)	ASHA ANC visits Occasionally/ Regularly n=928 (60.3%)	P-value
Latent Classes			0.1391			0.4133
Class 1	131 (50.8%)	575 (45.2%)		303 (44.5%)	403 (47.4%)	
Class 2	32 (12.4%)	230 (18.1%)		122 (17.9%)	140 (16.5%)	
Class 3	59 (22.9%)	293 (23.0%)		167 (24.5%)	185 (21.8%)	
Class 4	36 (14.0%)	175 (13.8%)		89 (13.1%)	122 (14.4%)	
Age Categories			0.8109			0.2133
<20 years	58 (22.5%)	303 (23.8%)		174 (25.6%)	187 (22.0%)	
20-24 years	165 (64.0%)	813 (63.9%)		428 (62.9%)	550 (64.7%)	
≥ 25 years	35 (13.6%)	157 (9.3%)		79 (11.6%)	113 (13.3%)	
Delivery Location			0.2455			0.2629
Home	4 (1.6%)	8 (0.6%)		6 (0.9%)	6 (0.7%)	
Sub-center/ Primary Health Center/District Health	137 (53.3%)	652 (51.4%)		366 (54.0%)	423 (50.0%)	
Maternity Hospital/Private Nursing Home	116 (45.1%)	607 (47.9%)		306 (45.1%)	417 (49.3%)	
Baseline Sexually Transmitted Infections			0.4719			0.0054*
No	239 (93.7%)	1161 (92.4%)		632 (94.8%)	768 (91.0%)	

Yes	16 (6.3%)	95 (7.6%)		35 (5.3%)	76 (9.0%)	
Previous Stillbirth or Neonatal Loss			0.3094			0.7281
No	245 (95.0%)	1226 (96.3%)		653 (95.9%)	818 (96.2%)	
Yes	13 (5.0%)	47 (3.7%)		28 (4.1%)	32 (3.8%)	
History of Spontaneous Abortion			0.0200 *			0.7388
No	222 (86.1%)	1156 (90.8%)		611 (89.7%)	767 (90.2%)	
Yes	36 (14.0%)	117 (9.2%)		70 (10.3%)	83 (9.8%)	
History of Induced Abortion			0.7157			0.3863
No	251 (97.3%)	1233 (96.9%)		663 (97.4%)	821 (96.6%)	
Yes	7 (2.7%)	40 (3.1%)		18 (2.6%)	29 (3.4%)	
Passive Smoking			0.3453			0.2726
No	206 (79.8%)	1048 (82.3%)		566 (83.1%)	688 (80.9%)	
Yes	52 (20.2%)	225 (17.7%)		115 (16.9%)	162 (19.1%)	
Previous Low Birth Weight			0.0521			0.1873
No	200 (77.5%)	1052 (81.8%)		547 (80.3%)	705 (82.9%)	
Yes	58 (22.5%)	221 (17.4%)		134 (19.7%)	145 (17.1%)	
Frequency of ANC Visits			0.0340 *			<0.0001* *
<8 visits	118 (19.3%)	140 (15.2%)		335 (49.2%)	275 (32.4%)	
≥ 8 visits	492 (80.7%)	781 (84.8%)		346 (50.8%)	575 (67.7%)	
Baseline Anemia Status			0.4840			0.2216

Normal (>11 g/dl)	59 (22.9%)	312 (24.5%)		156 (22.9%)	215 (25.3%)	
Mild (10.0-10.9 g/dl)	47 (18.2%)	262 (20.6%)		150 (22.0%)	159 (18.7%)	
Moderate/Severe (≤ 9.9 g/dl)	152 (58.9%)	699 (54.9%)		375 (55.1%)	476 (56.0%)	
History of Hypertension			0.8859			0.0120*
No	253 (98.1%)	1250 (98.2%)		662 (97.2%)	841 (98.9%)	
Yes	5 (1.9%)	23 (1.8%)		19 (2.8%)	9 (1.1%)	
Baseline Hypertension			0.0058*			<0.0001**
Normal (<120/80 mm Hg)	171 (66.3%)	743 (58.4%)		452 (66.4%)	462 (54.4%)	
Pre-hypertension (120-139 mm Hg/ 0r 80-89 mm Hg)	76 (29.5%)	499 (39.2%)		208 (30.5%)	367 (43.2%)	
Hypertension (>140/>90 mm/Hg)	11 (4.3%)	31 (2.4%)		21 (3.1%)	21 (2.5%)	

**-<0.0001 *-<0.05

Table 3: Logistic Regression Models Examining the Interaction of ASHA and Latent Classes on Preterm Birth in rural Mysore District

Characteristics	**Model 1**	**Model 2**	**Model 3: Predictors and ASHA Home Visits Interaction**	**Model 4: Predictors and ASHA ANC visits Interaction**
	Unadjusted OR (95% CI)	**Adjusted OR (95% CI)**	**Adjusted OR (95% CI)**	**Adjusted OR (95% CI)**
Class				
Class 1 vs. Class 4	**1.79 (1.10–2.91)***	1.68 (1.00–2.83)	1.87 (0.91–3.83)	**1.83 (1.06–3.14)***
Class 2 vs. Class 4	1.35 (0.78–2.34)	1.35 (0.76–2.39)	1.67 (0.78–3.58)	1.45 (0.80–2.62)
Class 3 vs. Class 4	1.51 (0.83–2.75)	1.63 (0.85–3.12)	2.00 (0.87–4.60)	1.75 (0.90–3.43)
Age				
<20 years vs. ≥ 25 years	1.35 (0.78–2.35)	**1.92 (1.03–3.57)***	**1.94 (1.04–3.60)***	**1.89 (1.02–3.51)***
20-24 years vs. ≥ 25 years	1.21 (0.74–2.00)	1.46 (0.85–2.52)	1.46 (0.85–2.52)	1.45 (0.84–2.50)
Delivery Location				
Home vs Private Health Institution	2.66 (0.71–10.02)	1.73 (0.43–6.91)	1.73 (0.43–6.99)	1.79 (0.45–7.14)
Public vs. Private Health Institution	1.18 (0.86–1.60)	1.07 (0.77–1.48)	1.07 (0.77–1.48)	1.07 (0.77–1.48)
Baseline Sexually Transmitted Infection				
Yes vs. No	1.36 (0.79–2.34)	1.36 (0.78–2.37)	1.37 (0.78–2.39)	1.36 (0.78–2.37)
History of Neonatal Loss or Still Birth				
Yes vs. No	1.27 (0.61–2.61)	1.13 (0.53–2.39)	1.14 (0.54–2.42)	1.13 (0.53–2.39)
History of Spontaneous Abortion				
Yes vs. No	1.40 (0.88–2.23)	1.02 (0.58–1.79)	1.02 (0.58–1.80)	1.04 (0.59–1.83)
History of Induced Abortion				
Yes vs. No	0.64 (0.23–1.79)	0.50 (0.17–1.48)	0.51 (0.17–1.51)	0.51 (0.17–1.51)
Passive Smoking				
Yes vs. No	1.08 (0.73–1.60)	1.05 (0.70–1.59)	1.05 (0.70–1.59)	1.07 (0.71–1.61)
Previous Low Birth Weight				

Yes vs. No	**1.60 (1.12–2.29)***	1.38 (0.88–2.17)	1.37 (0.87–2.15)	1.37 (0.87–2.15)
Anemia				
Mild vs. Normal	0.59 (0.35–1.00)	**0.56 (0.33–0.96)***	**0.56 (0.33–0.96)***	**0.56 (0.33–0.96)***
Moderate/Severe vs. Normal	1.13 (0.78–1.62)	1.09 (0.75–1.59)	1.10 (0.75–1.60)	1.10 (0.75–1.60)
History of Hypertension				
Yes vs. No	1.59 (0.60–4.23)	1.17 (0.41–3.28)	1.14 (0.40–3.20)	1.04 (0.37–2.93)
Hypertension				
Pre-hypertension (120-139 mm Hg/ 0r 80-89 mm Hg) vs. Normal	1.18 (0.86–1.62)	1.27 (0.91–1.78)	1.30 (0.93–1.81)	1.28 (0.92–1.78)
Hypertension (>140/>90 mm/Hg) vs. Normal	**2.16 (1.01–4.64)***	2.18 (0.97–4.90)	2.17 (0.96–4.89)	2.21 (0.98–4.97)
Antenatal Checkups				
<8 visits vs. ≥ 8 visits	**1.48 (1.09–2.01)***	1.36 (0.98–1.89)	1.35 (0.98–1.87)	1.36 (0.98–1.88)
ASHA Home Visits During Pregnancy				
Never/Rarely vs. Occasionally/Regularly	**1.58 (1.09–2.29)***	1.52 (0.97–2.38)	1.47 (0.92–2.36)	
ASHA-accompanied ANC Visits				
Never/Rarely vs. Occasionally/Regularly	1.11 (0.82-1.51)	0.95 (0.65–1.39)		1.10 (0.75–1.61)
INTERACTIONS				
Class*ASHA Home Visits				
Class 1 vs. Class 4*ASHA Home Visits (Never/Rarely)			2.14 (0.58–7.90)	
Class 2 vs. Class 4*ASHA Home Visits (Never/Rarely)			2.35 (0.59–9.40)	
Class 3 vs. Class 4*ASHA Home Visits (Never/Rarely)			2.76 (0.63–12.03)	
Class 1 vs. Class 4 *ASHA Home Visits (Occasionally/Regularly)			1.63 (0.93–2.85)	
Class 2 vs. Class 4*ASHA Home Visits (Occasionally/Regularly)			1.19 (0.63–2.29)	
Class 3 vs. Class 4*ASHA Home Visits (Occasionally/Regularly)			1.45 (0.70–2.96)	
Class*ASHA-accompanied ANC Visits				
Class 1 vs. Class 4*ASHA-accompanied ANC Visits (Never/Rarely)				**2.62 (1.12–6.12)***
Class 2 vs. Class 4*ASHA-accompanied ANC Visits (Never/Rarely)				2.07 (0.83–5.17)
Class 3 vs. Class 4*ASHA-accompanied ANC Visits (Never/Rarely)				**3.47 (1.31–9.15)***
Class 1 vs. Class 4*ASHA-accompanied ANC Visits (Occasionally/Regularly)				1.28 (0.67–2.43)

Class 2 vs. Class 4*ASHA-accompanied ANC Visits (Occasionally/Regularly)	1.02 (0.49–2.11)
Class 3 vs. Class 4*ASHA-accompanied ANC Visits (Occasionally/Regularly)	0.88 (0.37–2.14)

CI, confidence intervals; OR, odds ratio; Bolded point estimates indicate statistical significance at P <0.05*
Model 2: Adjusted for age, delivery location, baseline STI, history of neonatal loss or still birth, history of spontaneous abortion, history of induced abortion, passive smoking, previous low birth weight, anemia, history of hypertension, hypertension, ANC visits, ASHA home visits during pregnancy and ASHA-accompanied visits.
Model 3: Adjusted for age, delivery location, baseline STI, history of neonatal loss or still birth, history of spontaneous abortion, history of induced abortion, passive smoking, previous low birth weight, anemia, history of hypertension, hypertension, ANC visits, ASHA home visits during pregnancy and interaction of classes and ASHA home visits during pregnancy.
Model 4: Adjusted for age, delivery location, baseline STI, history of neonatal loss or still birth, history of spontaneous abortion, history of induced abortion, passive smoking, previous low birth weight, anemia, history of hypertension, hypertension, ANC visits, ASHA home visits during pregnancy and interaction of classes and ASHA-accompanied ANC visits.
Class 1: “Low SES, Early Marriage, Multigravida, 1 Child or More”, Class 2 “Low SES, Later Marriage, Primigravida, No Children”, Class 3 “High SES, Later Marriage, Multigravida, 1 Child or More” and Class 4 “High SES, Later Marriage, Primigravida, No Children”

Table 4: Logistic Regression Models Examining the Interaction of ASHA and Latent Classes on Low Birth Weight in rural Mysore District

Characteristics	Model 1	Model 2	Model 3: Predictors and ASHA Home Visits Interaction	Model 4: Predictors and ASHA ANC Visits Interaction
	Unadjusted OR (95% CI)	**Adjusted OR (95% CI)**	**Adjusted OR (95% CI)**	**Adjusted OR (95% CI)**
Class				
Class 1 vs. Class 4	**1.75 (1.08–2.84)***	1.31 (0.78–2.18)	1.57 (0.70–3.57)	1.30 (0.78–2.18)
Class 2 vs. Class 4	**2.83 (1.71–4.71)***	**2.46 (1.46–4.15)***	**3.11 (1.35–7.13)***	**2.47 (1.47–4.17)***
Class 3 vs. Class 4	1.13 (0.60–2.12)	0.89 (0.45–1.75)	0.75 (0.25–2.26)	0.88 (0.44–1.73)
Age				
<20 years vs. ≥ 25 years	1.08 (0.67–1.75)	0.99 (0.58–1.71)	1.02 (0.59–1.74)	1.00 (0.58–1.71)
20-24 years vs. ≥ 25 years	0.85 (0.55–1.32)	0.97 (0.60–1.54)	0.98 (0.61–1.57)	0.97 (0.61–1.55)
Delivery Location				
Home vs Private Health Institution	1.45 (0.31–6.74)	1.55 (0.32–7.49)	1.53 (0.31–7.48)	1.55 (0.32–7.52)
Public vs. Private Health Institution	1.31 (0.97–1.75)	1.27 (0.93–1.73)	1.28 (0.94–1.74)	1.27 (0.93–1.73)
Baseline Sexually Transmitted Infection				
Yes vs. No	1.41 (0.85–2.34)	1.48 (0.87–2.51)	1.50 (0.88–2.53)	1.49 (0.88–2.51)
History of Neonatal Loss or Still Birth				
Yes vs. No	**1.92 (1.04–3.55)***	1.65 (0.86–3.17)	1.67 (0.87–3.21)	1.65 (0.86–3.18)
History of Spontaneous Abortion				
Yes vs. No	1.31 (0.84–2.06)	0.96 (0.56–1.66)	0.95 (0.56–1.64)	0.96 (0.56–1.65)
History of Induced Abortion				
Yes vs. No	0.70 (0.28–1.79)	0.65 (0.25–1.77)	0.62 (0.23–1.67)	0.65 (0.24–1.75)
Passive Smoking				
Yes vs. No	**1.46 (1.03–2.07)***	1.37 (0.95–1.99)	1.37 (0.94–1.98)	1.37 (0.95–1.99)
Previous Low Birth Weight				
Yes vs. No	**1.74 (1.24–2.43)***	**2.17 (1.41–3.34)***	**2.21 (1.44–3.40)***	**2.19 (1.42–3.37)***
Anemia				

Mild vs. Normal	0.97 (0.64–1.47)	0.95 (0.62–1.47)	0.95 (0.61–1.46)	0.95 (0.61–1.43)
Moderate/Severe vs. Normal	0.75 (0.53–1.06)	0.71 (0.50–1.03)	0.71 (0.49–1.02)	0.71 (0.50–1.03)
History of Hypertension				
Yes vs. No	1.04 (0.36–3.03)	0.96 (0.32–2.90)	1.00 (0.33–3.01)	0.98 (0.32–2.98)
Hypertension				
Pre-hypertension (120-139 mm Hg/ 0r 80-89 mm Hg) vs. Normal	1.01 (0.75–1.36)	1.01 (0.73–1.39)	0.99 (0.72–1.36)	1.01 (0.74–1.39)
Hypertension (>140/>90 mm/Hg) vs. Normal	0.65 (0.23–1.85)	0.69 (0.24–2.03)	0.72 (0.25–2.13)	0.69 (0.24–2.04)
Antenatal Checkups				
<8 visits vs. ≥ 8 visits	1.23 (0.92–1.65)	1.17 (0.85–1.60)	1.20 (0.88–1.64)	1.17 (0.85–1.60)
ASHA Home Visits During Pregnancy				
Never/Rarely vs. Occasionally/Regularly	1.11 (0.76–1.63)	0.99 (0.63–1.65)	0.82 (0.46–1.47)	
ASHA-accompanied ANC Visits				
Never/Rarely vs. Occasionally/Regularly	1.22 (0.91–1.64)	1.16 (0.82–1.65)		1.18 (0.81–1.72)
INTERACTIONS				
Class*ASHA Home Visits				
Class 1 vs. Class 4*ASHA Home Visits (Never/Rarely)			2.07 (0.45–9.53)	
Class 2 vs. Class 4*ASHA Home Visits (Never/Rarely)			4.30 (0.90–20.52)	
Class 3 vs. Class 4*ASHA Home Visits (Never/Rarely)			0.59 (0.08–4.62)	
Class 1 vs. Class 4 *ASHA Home Visits (Occasionally/Regularly)			1.20 (0.70–2.06)	
Class 2 vs. Class 4*ASHA Home Visits (Occasionally/Regularly)			**2.24 (1.29–3.92)***	
Class 3 vs. Class 4*ASHA Home Visits (Occasionally/Regularly)			0.96 (0.48–1.95)	
Class*ASHA-accompanied ANC Visits				
Class 1 vs. Class 4*ASHA-accompanied ANC Visits (Never/ Rarely)				1.11 (0.55–2.24)
Class 2 vs. Class 4*ASHA-accompanied ANC Visits (Never/Rarely)				**2.26 (1.10–4.63)***
Class 3 vs. Class 4*ASHA-accompanied ANC Visits (Never/Rarely)				0.71 (0.27–1.89)
Class 1 vs. Class 4*ASHA-accompanied ANC Visits (Occasionally/Regularly)				1.53 (0.74–3.15)

Class 2 vs. Class 4*ASHA-accompanied ANC Visits (Occasionally/Regularly)	**2.70 (1.27–5.74)***
Class 3 vs. Class 4*ASHA-accompanied ANC Visits (Occasionally/Regularly)	1.08 (0.43–2.70)

CI, confidence intervals; OR, odds ratio; Bolded point estimates indicate statistical significance at P <0.05*
Model 2: Adjusted for age, delivery location, baseline STI, history of neonatal loss or still birth, history of spontaneous abortion, history of induced abortion, passive smoking, previous low birth weight, anemia, history of hypertension, hypertension, ANC visits, ASHA home visits during pregnancy and ASHA-accompanied ANC visits.
Model 3: Adjusted for age, delivery location, baseline STI, history of neonatal loss or still birth, history of spontaneous abortion, history of induced abortion, passive smoking, previous low birth weight, anemia, history of hypertension, hypertension, ANC visits, ASHA home visits during pregnancy and interaction of classes and ASHA home visits during pregnancy.
Model 4: Adjusted for age, delivery location, baseline STI, history of neonatal loss or still birth, history of spontaneous abortion, history of induced abortion, passive smoking, previous low birth weight, anemia, history of hypertension, hypertension, ANC visits, ASHA home visits during pregnancy and interaction of classes and ASHA-accompanied ANC visits.
Class 1: “Low SES, Early Marriage, Multigravida, 1 Child or More”, Class 2 “Low SES, Later Marriage, Primigravida, No Children”, Class 3 “High SES, Later Marriage, Multigravida, 1 Child or More” and Class 4 “High SES, Later Marriage, Primigravida, No Children

MANUSCRIPT 3

Examining the mediating role of anemia between sociodemographic factors and Preterm Birth and Low Birth Weight

Abstract

Background

The prevalence of anemia among pregnant women in India is 60%. Maternal anemia is thought to be a cause of preterm birth and low birth weight. However, few studies have examined the mediating role anemia on adverse birth outcomes. Therefore, the objective of this study was to examine the mediating role of anemia in the relationship of socioeconomic status (SES) and preterm birth and low birth weight.

Methods

We analyzed secondary data from a prospective cohort study conducted between 2011-2014 among 1540 pregnant women. Latent Class Analysis was conducted to identify distinct socioeconomic classes. Logistic regression modeling was performed to examine the relationship between SES latent classes and preterm birth and low birth weight. Employing causal mediation, we examined the mediating role of anemia on the relationship between SES latent classes and preterm birth and low birth weight.

Results

Two classes were identified: Class 1 "low SES and early marriage" and Class 2 "high SES and later marriage." Women in Class 1 had higher odds of low birth weight (adjusted Odds Ratio [aOR]: 2.12, 95% Confidence Interval [CI]: 1.36-3.31) compared to women in Class 2. The findings showed no significant effects (total, direct or indirect

effects) of Class 1 on preterm birth. The analysis showed that the total effect on low birth weight (aOR: 2.08, 95% CI: 1.41-3.14) was statistically significant and independent of anemia. The direct effect of Class 1 on low birth weight (aOR: 2.11, 95% CI: 1.43-3.45) but not the indirect effects (aOR: 0.99, 95% CI: 0.95-1.00.) was statistically significant.

Conclusion

Our findings indicate that being socioeconomically disadvantaged (Class 1: "low SES and early marriage") was associated with low birth weight, but that this relationship was not mediated by anemia. Despite not finding a mediation effect for the association between SES and adverse birth outcomes, anemia has been directly associated with low birth weight and preterm birth in numerous studies. Thus, given the high prevalence of anemia among pregnant women in India particularly those living in low SES communities, there needs to be tailored interventions to reduce the rates of anemia and ultimately improve birth outcomes and reduce disparities among rural populations in India.

Keywords: Anemia, preterm birth, low birth weight, mediation

Introduction

Preterm birth and low birth weight are important leading causes for neonatal morbidity and mortality. Globally, nearly 15 million babies are born preterm (before 37 weeks of completed gestation), and 10 million babies are born with low birth weight (weighing less than 2500g) each year (World Health Organization 2018a; Blencowe et al. 2013). Preterm birth is currently the leading cause of deaths for children under 5 years old worldwide (Liu et al. 2016). Despite concerted efforts in improving maternal and newborn health, India consistently has the highest number of preterm and low birth weight births (3.5 and 7.5 million respectively) in the world (World Health Organization 2012; Sankar et al. 2016). Of all births in India, approximately 13% are preterm births and 28% are low birth weight babies (Every Preemie Scale 2019). These adverse birth outcomes resulted in 700,000 neonatal deaths annually and account for more than a quarter of the global neonatal deaths (Liu et al. 2019; Sankar et al. 2016). Additionally, being preterm or with a low birth weight can lead to complications including visual and hearing impairment, respiratory distress, neonatal sepsis, neurodevelopmental delays, and chronic health conditions later in adulthood (Undela et al. 2019b; Ministry of Health & Family 2013-2015). Identifying the pregnancy-related driving factors of preterm birth and low birth weight is critically important for early risk detection, prevention, and timely treatment to prevent infant morbidity and mortality.

Evidence from systematic reviews and meta-analyses have demonstrated that lower socioeconomic status (SES) is associated with poor birth outcomes specifically among marginalized communities globally (Blumenshine et al. 2010; Ghimire et al. 2018b). Lower income, poor education, and unemployment have been linked to adverse birth outcomes in India (Kader and Perera 2014; Ghimire et al. 2018b). Low SES results in lack of access to quality obstetric services (Kumar et al. 2019), limited access to healthy nutrition or nutritional deficiencies (Varadharajan, Thomas, and Kurpad 2013), and low utilization of healthcare services in India (Kumar et al. 2019). These outcomes contribute to a high rate of preterm and low birth weight outcomes in rural settings in India. While there have been numerous studies that provide evidence on the association between SES and adverse birth outcomes, there is little literature on the causal mechanisms driving the association between SES and preterm birth or low birth weight.

It has been speculated that anemia may be in the causal pathway of preterm birth and low birth weight (Parks et al. 2019). Anemia is caused by nutritional deficiencies, parasitic and bacterial infections, and in-born red blood cells disorders i.e. thalassemia (Breymann 2015). Specifically, nutritional iron-deficiency anemia, may cause preterm birth through several mechanisms including hypoxia, oxidative stress, and infections (Scholl 2005; Allen 2001). Hypoxia, characterized by inadequate oxygen transfer from the mother to fetus can induce maternal and fetal stress, activating the release of the corticotropin-releasing hormone resulting in preterm delivery (Zhang et al. 2009). Secondly, increased oxidative stress may result in free radicals and oxidative molecules leading to maternal-fetal cellular damage leading to preterm delivery (Allen 2001). Lastly, infections and inflammation may result in cytokine production inducing preterm labor (Allen 2001). Given all these multiple mechanisms, we wanted to explore the causal relationship of anemia and adverse birth outcomes.

Moreover, the prevalence of anemia in India among pregnant women is 60% (Siddiqui et al. 2017). Specifically, the most recent National Family Health Survey (2019-2020) reported in Karnataka state that anemia disproportionately impacts pregnant women from rural regions and tribal communities compared to urban areas (prevalence among pregnant women of 50.6% vs. 30.4% respectively) (International Institute of Population Health Sciences 2019-2020). Particularly, factors associated with anemia in lower SES communities are undernutrition, lower body mass index, and poor uptake of iron-folic acid supplementation (International Institute of Population Health Sciences 2016; Ali et al. 2020; Thankachan et al. 2007). Although the Indian government recommends nutritious food and a daily pill of iron-folic acid supplementation during pregnancy, a national survey reported that only 30% of pregnant women took the pill during the recommended 100 days after the first trimester (International Institute of Population Health Sciences 2016). Consequently, this low adherence may lead to adverse birth outcomes such as preterm birth, small for gestational age, low birth weight, and perinatal mortality (Rahman et al. 2016). Due to the high prevalence of anemia and its impact on adverse birth outcomes, it is critical to examine its role on preterm birth and low birth weight in rural India. Examining the causal mechanisms is vital in understanding if anemia mediates the relationship between SES disparities and preterm birth and low birth weight. This understanding will ultimately guide the implementation of targeted interventions and policies to improve health outcomes among socioeconomically disadvantaged communities. Therefore, we sought to examine the mediating role of anemia in the relationship of SES and preterm birth and low birth weight.

Materials and Methods

Study Setting and Dataset

The data for the current study is from the Saving Children Improving Lives (SCIL) study—a prospective cohort study conducted between 2011-2014 among pregnant women from rural Mysore District, located in the state of Karnataka in Southern India. In Mysore, nearly 60% of the population resides in rural areas, and the literacy rate among women is 67% compared to 78% for men ('Mysore District : Census 2011 data' Census 2011). The original SCIL study objective assessed the feasibility of integrated antenatal care and HIV testing among pregnant women and was approved by the institutional review boards of Florida International University in Miami, Florida and

Public Health Research Institute of India (PHRII) in Mysore, India. Further details of the protocol have been published elsewhere (Kojima et al. 2017).

Utilizing mobile medical clinics, 1820 pregnant women in Mysore District were provided integrated antenatal care and HIV testing. These women were informed about the study during an educational and awareness program hosted in each of the villages where the program was conducted. The next day, the medical team visited the village to run the mobile clinics. Women who were interested in participating in the study were screened for eligibility. The inclusion criteria included residing in a village in Mysore district for more than 6 months, being pregnant, and having the capacity to participate in an informed consent process. The trained research staff at the PHRII administered a survey to each participant after completion of the informed consent in the local language of *Kannada*. The survey included questions on sociodemographics, medical, and reproductive history. A detailed physical exam along with routine antenatal laboratory examinations of urine and blood were conducted. All laboratory evaluations were performed by trained laboratory technicians at PHRII.

All women enrolled in the study had three follow-up visits. The first follow-up visit occurred within 15 days of delivery. The subsequent follow-up visits occurred 6 months and 12 months after delivery. Women aged 18 years and older and those who had a live birth were included in our analysis. We excluded 98 individuals who had a fetal death and 40 individuals with a missing date on last menstrual period. Our final total sample was 1,540 women.

Exposure Variables

The predictor variables were latent classes of SES factors derived from latent class analysis (LCA) using SAS/STAT v15.2 PROC LCA (Lanza et al. 2007) which included participant's education, age at marriage, total monthly household income, and partner's occupation. Participant's education was categorized as primary education or less (<8 years of education), secondary education (9-10 years of education), and upper secondary education or higher (>10 years of education or higher). Age at marriage was categorized as less than 18 years old or 18 years and older. Total monthly household income was categorized as <4000 Indian Rupees, 4000-10,000 Indian Rupees and >10,000 Indian rupees. Partner's occupation was categorized as unemployed, unskilled, semi-skilled or skilled, and professional. Participant's occupation was not available in the data given that majority of Indian women are homemakers and female paid employment in rural India is low (Srivastava and Srivastava 2010). In our study, approximately 93% of the women's occupation was missing in the dataset due to item non-response and therefore was excluded in the LCA.

We assessed model comparison approach in the LCA procedure by testing 2-6 latent classes. We selected the number of classes based on the model fit statistics including, Bayesian Information Criterion (BIC), adjusted Bayesian Information Criterion (aBIC), Adjusted Information Criterion (AIC), and entropy. A lower BIC, aBIC and AIC indicate a better model fit, while the entropy value close to 1.0 indicates a better distinction of classes (Nylund-Gibson and Choi 2018). The participants were assigned to their respective classes based on the highest posterior membership.

Mediator

The mediator variable, anemia, was dichotomous (yes or no) and defined as hemoglobin concentration of ≤10.0 g/dl which corresponds to moderate or severe anemia based on the World Health Organization classification (World Health Organization 2011b). The measure was collected during baseline study assessment.

Outcome

The outcomes of interest were preterm birth and low birth weight. Preterm birth was defined as live singleton birth delivery before 37 completed weeks of gestation based on the last menstrual period (World Health Organization 2018a), while low birth weight was defined as infant born weighing less than 2500 grams (World Health Organization 2004). The outcomes were collected 15 days after delivery.

Covariates

The covariates were chosen based on prior literature review on maternal obstetric factors (Blencowe et al. 2013). Participant's age was categorized as less than 20 years old, 20-24 years and 25 years or older at baseline of the study. Maternal obstetric characteristics were dichotomous (yes or no) and were self-reported. These obstetric measures included exposure to passive smoking and number of previous pregnancies categorized as 0 pregnancies, 1-2 pregnancies, and 3 or more pregnancies. Sexually transmitted infections measurement was dichotomized as yes or no collected at baseline of the study. The covariates were collected during the baseline of the study.

Statistical Analysis

We calculated descriptive statistics to examine the characteristics of the pregnant women in the study. Chi-square tests were performed to examine the association between maternal SES latent classes, and anemia and preterm birth and low birth weight.

Next, we applied logistic regression modeling to examine the relationship between SES latent classes and preterm birth and low birth weight. Lastly, a causal mediation analysis using the SAS PROC CAUSAL MED (Stokes and Staff) procedure was performed to examine the mediating role of anemia on the relationship between SES latent classes and preterm birth and low birth weight. This procedure utilizes the counterfactual framework based on the Valeri and Vanderwheele (Valeri and VanderWeele 2013) approach to decompose the total effect of selected latent class into indirect effects (mediated by anemia) and direct effects. The natural direct effect corresponds to the change in outcome (preterm birth or low birth weight) by the exposure (selected latent class) given that the mediator remained unchanged. The natural indirect effect can be explained by the expected change in the outcome (preterm birth or low birth weight) from a change in the mediator (anemia). We tested interactions between the exposure (selected latent class) and mediator (anemia). The PROC CAUSALMED procedure generated odds ratio and 95% confidence intervals (CIs) utilizing the maximum likelihood estimates. In addition, we applied the bootstrapping approach using the percentile method with 1000 replications to test for significance in the mediation by determining if zero is not contained within the CIs.

Results

Based on the model fit statistics (aBIC: 165.38, entropy 0.59), we selected two classes, one “high SES and later marriage”, and the other “low SES and early marriage”. The “high SES and later marriage” class was characterized by a higher probability to have a secondary education or higher, being married 18 years and older, monthly household income 4000 INR or higher, and partner having a semi-skilled, skilled or professional occupations. The “low SES and early marriage” was characterized by a higher probability of having a primary education or less, being married less than 18 years old, monthly household income less than 4000 INR, partner being unemployed or having unskilled occupation. The women were categorized in these classes according to the highest posterior probability of membership, and thus, the final exposure variable was a dichotomous variable where “low SES and later marriage” was the exposure, and the “high SES/early marriage” was the reference group.

Table 1 shows the descriptive characteristics of the SES latent classes of the women in the study. Approximately 79% of the women belonged to Class 1 “Low SES and early marriage.” Of these women, nearly half received a primary education or less (≤8 years of education), 47% were married before reaching 18 years old, nearly 40% earned a monthly household income of <4,000 Indian Rupees, and 23% of their partner’s occupation were unskilled. Approximately 21% of the women belonged to Class 2 “High SES and later marriage.” In this class, 88% had completed secondary education or higher (>10 years of education), 90% had married after 18 years of age, only 20% earned a monthly household income of <4,000 Indian Rupees, and 70% of their partner’s occupation were semi-skilled or skilled while 15% were professionals.

Table 2 indicates the univariate analysis between the latent classes and covariates on anemia, preterm birth and low birth weight. A higher proportion of women who had anemia belonged to Class 1, were between the ages of 20-24 years old, had 1 or more prior pregnancies and had exposure to passive smoking. A higher proportion of women who had delivered a preterm infant belonged to Class 1 “low SES and early marriage”, were between the ages of 20-24 years old, had 1 or more prior pregnancies, and had exposure to passive smoking. A higher proportion of women who delivered a low birth weight infant belonged to Class 1, were between the ages of 20-24 years old, had 1 or more prior pregnancies, and had exposure to passive smoking. Table 3 depicts the logistic regression output between exposure and mediator, exposure and outcomes, and mediator and outcomes. In the unadjusted analysis, women with anemia had a higher odds of preterm birth (odds ratio: 1.40, 95% confidence interval [CI]: 1.03-1.93). After adjusting for the covariates, the association was no longer significant. Women in Class 1 "low SES and early marriage" had higher odds of low birth weight (adjusted Odds Ratio [aOR]: 2.12, 95% CI: 1.36-3.31) compared to women in Class 2 "high SES and later marriage." Women with previous pregnancies had higher odds of preterm birth; 1-2 pregnancies (aOR: 1. 1.60, 95% CI: 1.10-2.34) and 3 or more pregnancies (aOR: 2.74, 95% CI: 1.29-5.84) compared to primigravida women. Women with 1 or more pregnancies had lower odds of low birth weight (aOR: 0.70, 95% CI: 0.50-0.98) compared to primigravida women.

Figures 1 and 2 show the causal mediating relationship of anemia in the relationship between the latent classes and preterm birth and low birth weight respectively. There were no significant associations observed for the interaction term so the interaction was removed. The findings showed no significant total effects of Class 1 "low SES and early marriage" on preterm birth. The decomposition into direct and indirect effects indicated that there was no significant direct effect of SES on preterm birth and no mediation by anemia. There was a significant total effect of SES on low birth weight (aOR: 2.08, 95% CI: 1.41-3.14) which was independent of anemia. The direct effect of Class 1 on low birth weight was significant (aOR: 2.11, 95% CI: 1.43-3.45), but the indirect effect was not (aOR: 0.99, 95% CI: 0.95-1.00.)

Discussion

This study sought out to identify a causal mechanism of the relationship between SES and preterm birth or low birthweight infants which we hypothesized is anemia in rural India. Our findings suggest that being socioeconomically disadvantaged (Class 1: "low SES and early marriage") was associated with low birth weight, but this relationship was not mediated by anemia. Utilizing the causal mediation analysis, we found both significant total and direct effects on the relationship between SES and low birth weight for women in Class 1 compared to women in Class 2 ("high SES and later marriage"). However, there were no significant findings (total, direct, or indirect effects) observed for the causal pathway between the SES and preterm birth.

The total effects revealed a significant relationship between women in Class 1 "low SES and early marriage" and low birth weight. This includes all women regardless of anemia status, and shows an increased risk in low birth weight. Further, the direct effects showed a slightly more pronounced effect of the relationship between "low SES and early marriage" and low birth weight, compared to the total effects independent of anemia. In accordance with previous study findings in India, low SES and early marriage are often convoluted, due to the bi-directional relationship of early marriage, and lack of educational and employment opportunities (Scott et al. 2020; Raj et al. 2010b; Nguyen et al. 2019). Low SES coupled with early marriage, has been associated with undernutrition (Nguyen et al. 2019; Santhya et al. 2010), delayed contraception use (Santhya et al. 2010), unintended pregnancies (Godha, Hotchkiss, and Gage 2013), and inadequate maternal healthcare access (Nguyen et al. 2019; Godha, Hotchkiss, and Gage 2013; Santhya 2011), further leading to adverse birth outcomes including preterm birth, stillbirth, and low birth weight (Raj et al. 2010b; Santhya 2011). These findings underscore the need to have tailored and targeted interventions for women experiencing socioeconomic disadvantage and early marriage as we have observed its stronger association on low birth weight. Promoting an integrated service delivery approach in multi-sectoral entities that focuses on individual, community based, and government-based policies is vital in promoting healthy pregnancies (Lawn et al. 2014).

Prior literature has shown the association between socioeconomic status and anemia on poor birth outcomes in India (Ali et al. 2020; Kumari et al. 2019) . However, in our study we did not find a significant relationship between socioeconomically disadvantaged groups and anemia or a mediating role of anemia in causal pathway of "low SES and early marriage" and preterm birth or low birth weight. The majority of population in our study comprised of low SES therefore there was not a broad enough to examine the full effect of SES. Hence we were not able to observe a significant association. Additionally, other factors besides anemia might play a significant role as a mediator on the causal pathway. Existing literature supports that possible mediators for preterm birth may be infectious diseases such as urinary tract infection, or bacterial infections, and vascular disease (Blencowe et al. 2013; Goldenberg et al. 2008). Tchirikov and colleagues recently conducted an integrative review that documented premature rupture of membranes, leading to spontaneous preterm birth, may have multi-factorial causes including bacterial products and/or pro-inflammatory cytokines (Tchirikov et al. 2018). Since we did not have biomarker data, we could not assess the role of these factors on preterm birth. Moreover, pregnant women with greater social disadvantage are more likely to have chronic diseases compared to women with lesser social disadvantage, increasing the risks of negative birth outcomes (Gavin, Nurius, and Logan-Greene 2012). However, it is worth mentioning that the average age of this study sample was 21.6 years old; hence the majority of the women were relatively young. Therefore, chronic diseases might not play a role in the causal pathway in our study population. This warrants further investigation to examine multiple possible risk factors within the causal pathway of low SES and preterm birth or low birth weight.

While there was no significant mediation observed in the study, there is still a high prevalence of anemia among Indian pregnant women (80.7%) in Class 1, that may contribute to preterm birth or low birth weight. In our unadjusted analysis findings, we observed a significant relationship between anemia and preterm birth. Similarly, the relationship between anemia and adverse birth outcomes is well-documented (Parks et al. 2019; Bora et al. 2014; Kidanto et al. 2009). However, there have been conflicting findings based on the association of anemia and birth outcomes according to the timing of pregnancy. A systematic review by Dewey and Oaks highlighted that anemia, characterized by low hemoglobin concentrations is associated with adverse outcomes only in early pregnancy, but the observed relationship is often weaker in the second or the third trimester (Dewey and Oaks 2017). Zhang and colleagues also indicated that low hemoglobin during the third trimester was associated with reduced risk of spontaneous preterm labor (Zhang et al. 2009). Further sub-group analysis in our study indicated only 11% of the pregnant women received their hemoglobin concentration tests during their first trimester. Therefore, majority of our study sample participated in the study during their second and third trimester. This may be one of the potential reasons why our data denoted no mediation relationship. Further studies are needed to examine the relationship between anemic levels and preterm birth and low birth weight particularly by the specific trimester.

Given the high prevalence of anemia in our study, particularly in the “low SES and early marriage” class, there are several existing and new interventions worth mentioning to reduce the high anemia levels in pregnant women. Evidence-based interventions to address anemia during pregnancy have primarily been daily iron-folic acid (IFA) supplementation, nutrition, and fortified foods (Kapil and Bhadoria 2014). While nutritionists have encouraged IFA supplementation uptake, inadequate knowledge and socio-cultural beliefs have contributed to low adherence and uptake specifically in lower SES communities. Several studies have shown that side effects such as nausea and constipation, belief in medicine uptake during pregnancy, as well as lack of family support, and common misconceptions may serve as possible barriers (Mithra et al. 2014; Chatterjee and Fernandes 2014). Therefore, it is integral to conduct implementation science research to promote educational and informational awareness for women to understand the role of IFA supplementation, and its benefits for pregnant women and the fetus. Further, it is critical to conduct qualitative research i.e. key information interviews as well as focus groups to assess the barriers and facilitators of IFA uptake among rural pregnant women in India. This will be vital in understanding any cultural and context-specific recommendations needed to improve IFA uptake among rural women.

Healthy nutrition among pregnant mothers is vital to ensure optimal fetal growth and development. Nutritionists encourage consumption of healthy food sources including dark green leafy vegetables, beans, peanuts, sunflower seeds, fresh fruits, and fortification of food to achieve a balanced diet (Kapil and Bhadoria 2014). According to a systematic review and meta-analysis conducted by Imdad and Bhutta, protein-energy supplementation resulted in a 32% reduction in low birth weight and 38% reduction in stillbirth (Imdad and Bhutta 2011). Thus, it is critical to encourage evidence-based interventions that yield successful neonatal outcomes. Emerging interventions have recently incorporated mindfulness approaches and technological innovations to improve the diet among pregnant women. India has recently embraced food coaching apps to monitor and track nutritional value to improve calorie intake (Balakrishna, Ganesh, and Khosla 2021). However, it is critical to understand the efficacy of these programs and its feasibility on implementation in marginalized, tribal and rural regions in India, to ultimately reduce the prevalence of anemia and existing birth inequities.

The strengths of the study include the prospective cohort study design to examine the causal mediation pathway of "low SES and early marriage", anemia and preterm birth or low birth weight. The use of causal mediation approaches was advantageous in this study in understanding the causal pathways for preterm birth and low birth weight compared to the traditional logistic regression. Moreover, no study has examined the mediating role of anemia in the relationship between "low SES and early marriage" latent classes and preterm birth or low birth weight. Nonetheless, there were several limitations of the study. First, gestational age was based on the last menstrual period, since there was lack of ultrasound data in this predominantly rural setting. Second, anemia throughout pregnancy was not well-characterized since only the baseline measurement was taken, and the majority of the women who enrolled in the study were in the second and third trimesters. It remains vital to have multiple measures throughout pregnancy to evaluate the entire burden of anemia during fetal development. Furthermore, classification of anemia as <10 mg/dl may create misclassification bias since the measures were taken at different timepoints during pregnancy. Recent guidelines have classified anemia as hemoglobin concentration of less than 10.5 mg/dl in second and third trimesters attributed to the increase in plasma volume during pregnancy ('Good Clinical Practice Recommendations for Iron Deficiency Anemia in Pregnancy (IDA) in Pregnancy in India' 2011). Therefore, repeated measures taken throughout pregnancy with the appropriate measures is recommended for future studies. Moreover, the Indian guidelines recommends that all pregnant women receive IFA supplementation during pregnancy; however, prior studies have reported that uptake remains suboptimal due to a myriad of reasons including forgetfulness, unrealized need, possible side effects such as constipation, gastritis, and nausea (Pal et al. 2013; Varghese et al. 2019). Therefore, this may contribute to misclassification as well. In addition, we did not examine measures on biomarkers or inflammatory cytokines which may serve as potential mediators. Lastly, the dates of birth of the most recent previous pregnancy were missing; therefore, we could not assess the interpregnancy intervals (IPIs) as a potential mediator in our study, which may strongly affect anemia outcomes. It is worth mentioning that 37% of the women were primigravida, and IPIs may not impact their outcomes. Optimizing on adequate birth spacing may be an achievable modifier compared to significant changes in socioeconomic status in reducing preterm birth and low birthweight.

Conclusion

Our findings confirm the relationship between low socioeconomic status and early marriage and low birth weight. There was no mediating role of anemia in the relationship between the low socioeconomic status and early marriage and preterm or low birth weight. While our study did not observe a mediation effect of anemia in the association between SES and adverse birth outcomes, anemia has been directly associated with low birth weight and preterm birth in numerous studies. Given the high prevalence of anemia among pregnant women in low SES communities in rural India, IFA programs are critical; qualitive methodologies are needed to make IFA programs more effective among rural pregnant women in India. Moreover, there is a critical need to understand the socio-cultural barriers such as lack of social and familial support, negative side-effects, and misunderstandings about IFA uptake. Therefore, a comprehensive program evaluation may assist in findings adaptations that can increase uptake. Future studies should also explore possible mediators such as infections and inflammatory markers within the causal pathway of preterm birth and low birth weight.

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Tables and Figures

Table 1: Sociodemographic characteristics of rural pregnant women in Mysore District that were included to determine latent class membership (n=1540)

Maternal Characteristics	Latent Classes n (%) Class 1 :Low SES and Early Marriage 1212 (78.7%)	Latent Classes n (%) Class 2: High SES and Later Marriage 328 (21.3%)	P-Value
Pregnant Woman's Education			**<0.001**
Primary education or less (≤8 years)	603 (49.8%)	0 (0%)	
Secondary education (9-10 years)	588 (48.5%)	41 (12.50%)	
Upper Secondary and Higher (>10 years)	21 (1.7%)	287 (87.50%)	
Age at Marriage			**<.0001**
Less than 18 years old	66 (47.0%)	33 (10.06%)	
18 years and older	642 (53.0%)	295 (89.94%)	
Monthly household income (In Indian Rupees) (1 USD = 58.9 INR*)			**<.0001**
<4000	490 (40.4%)	64 (19.51%)	
4000-10,000	647 (53.4%)	172 (52.44%)	
>10,000	75 (6.2%)	92 (28.05%)	
Partner's Employment Categories			**<.0001**
Unemployed	5(0.4%)	2 (0.61%)	
Unskilled	283 (23.4%)	47 (14.33%)	
Semi-Skilled or Skilled	917 (75.7%)	231 (70.43%)	
Professional	7 (0.58%)	48 (14.63%)	

*The currency estimates are based on the time of the data collection period (2011-2014)

Table 2: Distribution of maternal obstetric characteristics of rural pregnant women in Mysore District, India (n=1540)

Maternal Characteristics	Anemia[a] Yes n=839 (55.1%)	Anemia[a] No n=685 (45.0%)	p-value	Preterm Birth[b] Yes n=187 (12.1%)	Preterm Birth[b] No n=1353 (87.9%)	p-value	Low Birth Weight[c] Yes n=213 (13.8%)	Low Birth Weight[c] No n=1327 (86.2%)	p-value
Latent Classes			0.063			0.061			**0.001**
Latent Class 1 (high SES/early marriage)	677 (80.7%)	526 (76.8%)		157 (84.0%)	298 (22.0%)		187 (87.8%)	1025 (77.2%)	
Latent Class 2 (low SES/later marriage)	162(19.3%)	159(23.2%)		30 (16.0%)	1055 (78.0%)		26 (12.2%)	302 (22.8%)	
Age Categories									
<20 years	200 (23.8%)	156 (22.8%)	0.682	48 (25.7%)	313 (23.1%)	0.565	57 (26.8%)	304 (22.9%)	0.368
20-24 years	538 (64.1%)	437 (63.8%)		119 (63.6%)	864 (63.9%)		127 (59.6%)	856 (64.5%)	
≥ 25 years	101(12.0%)	92 (13.4%)		20 (10.7%)	176 (13.0%)		29 (13.6%)	167 (12.6%)	
Reproductive Tract Infection(s)[d]									
Yes	67 (8.1%)	43 (6.4%)	0.199	17 (9.3%)	94 (7.0%)	0.261	20 (9.5%)	91 (7.0%)	0.184
No	762 (91.9%)	634 (93.7%)		165 (90.7%)	1243 (93.0%)		190 (90.5%)	1218 (93.0%)	

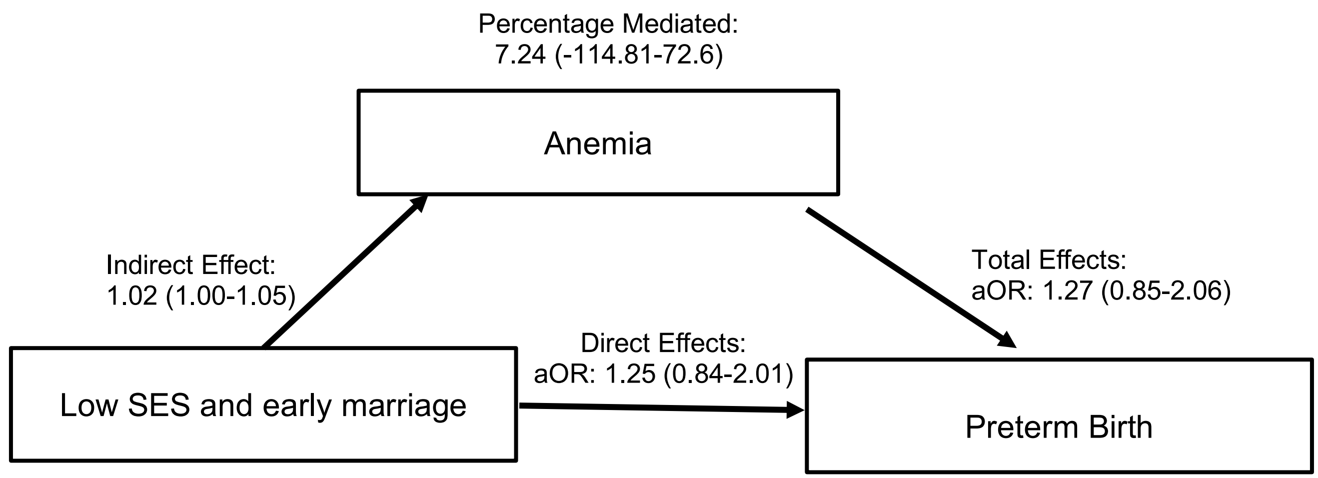
Total Previous Pregnancies									
0 prior pregnancies	302 (36.0%)	264 (38.5%)	0.457	54 (28.9%)	519 (38.4%)	**0.008**	90 (42.3%)	483 (36.4%)	**0.039**
1-2 pregnancies	503 (60.0%)	399 (58.3%)		121 (64.7%)	790 (58.4%)		111 (52.1%)	800 (60.3%)	
3 or more pregnancies	34 (4.0%)	22 (3.2%)		12 (6.4%)	44 (3.3%)		12 (5.6%)	44 (3.3%)	
Passive Smoking									
No	683 (81.4%)	564 (82.3%)	0.640	151 (80.8%)	1109 (82.0%)	0.686	163 (76.5%)	1097 (82.7%)	**0.031**
Yes	156 (18.6%)	121 (17.7%)		36 (19.3%)	244 (18.0%)		50 (17.9%)	230 (17.3%)	

a. Anemia is defined as hemoglobin concentration of <10 mg/dl or lower. Total n for Anemia is 1524.
b. Preterm Birth: <37 weeks of completed gestation
c. Low Birth Weight: weighing less than 2500 grams
d. Reproductive tract infections comprised of syphilis, hepatitis B, HIV and bacterial vaginosis

Table 3: Crude Odds Ratios and Adjusted Odds Ratios of class membership and anemia, preterm birth, and low birth weight by characteristics of rural pregnant women in Mysore District, India obtained from binary logistic regression output

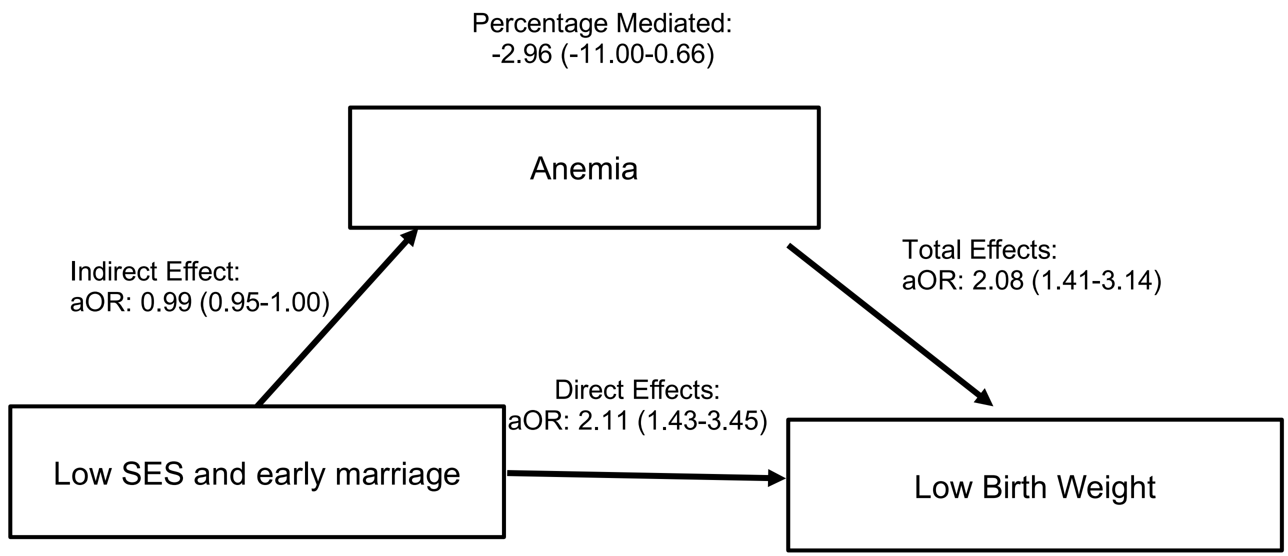
Maternal Characteristics	Anemia		Preterm Birth[c]		Low Birth Weight[d]	
	Crude Odds Ratio. (95% CI)	Adjusted Odds Ratio. (95% CI)	Crude Odds Ratio. (95% CI)	Adjusted Odds Ratio. (95% CI)	Crude Odds Ratio. (95% CI)	Adjusted Odds Ratio. (95% CI)
Latent Classes[a]						
Class 1 vs. 2	1.26 (0.99-1.62)	0.81 (0.62-1.04)	1.48 (0.98-2.23)	1.25 (0.81-1.92)	**2.12 (1.38-3.26)**	**2.12 (1.36-3.31)**
Anemia						
Yes vs. No	**--**	**--**	**1.41 (1.03-1.93)**	1.35 (0.98-1.86)	0.77 (0.59-1.03)	0.75 (0.55-1.00)
Age Categories (years)						
20-24 vs. <20	0.96 (0.75-1.23)	1.08 (0.82-1.40)	0.90 (0.63-1.29)	0.71 (0.48-1.06)	0.79 (0.56-1.11)	0.96 (0.66-1.40)
≥ 25 vs. <20	0.86 (0.60-1.22)	1.24 (0.85-1.80)	0.74 (0.43-1.29)	0.52 (0.28-0.94)	0.93 (0.57-1.51)	1.07 (0.64-1.81)
Baseline STI[b]						
Yes vs. No	1.30 (0.87-1.93)	0.78 (0.52-1.16)	1.36 (0.79-2.34)	1.34 (0.78-2.32)	1.41 (0.85-2.34)	1.37 (0.82-2.29)
Total Previous Pregnancies						
1-2 vs. 0	1.10 (0.89-1.36)	0.92 (0.73-1.16)	**1.47 (1.05-2.07)**	**1.60 (1.10-2.34)**	0.75 (0.55-1.01)	**0.70 (0.50-0.98)**
3 or more vs. 0	1.35 (0.77-2.37)	0.77 (0.43-1.38)	**2.62 (1.31-5.26)**	**2.74 (1.29-5.84)**	1.46 (0.74-2.88)	1.26 (0.62-2.56)
Passive Smoking						
Yes vs. No	1.06 (0.82-1.38)	0.95 (0.73-1.25)	1.08 (0.73-1.60)	1.02 (0.68-1.53)	**1.46 (1.03-2.07)**	1.37 (0.96-1.96)

a. Class 1: Low SES and early marriage; Class 2: High SES and later marriage
b. Baseline Sexually Transmitted Infection
c. Preterm Birth: <37 weeks of completed gestation
d. Low Birth Weight: weighing less than 2500 grams



Adjusted for age, baseline sexually transmitted infections, previous pregnancy(ies) and passive smoking

Figure 1: Schematic Causal Diagram of the mediating role of anemia in the association between socioeconomic status and preterm birth among rural pregnant women in Mysore District



Adjusted for age, baseline sexually transmitted infections, previous pregnancy(ies) and passive smoking

Figure 2: Schematic Causal Diagram of the mediating role of anemia in the association between socioeconomic status and low birth weight among rural pregnant women in Mysore District, India

CONCLUSIONS

The purpose of this dissertation was to examine the mediators, moderators, and high-risk latent classes of preterm birth and low birth weight among pregnant women in rural Mysore District, India. To our knowledge, this is the first study to employ LCA to examine the complex causal pathway of risks for pregnant women in rural tribal communities. Utilizing LCA as the central approach throughout this study, we identified high-risk classes of pregnant women for preterm birth and low birth weight and determined that belonging to a low SES latent class emerged as the strongest predictor for preterm birth and/or low birth weight across all three studies.

Our first study employed LCA on sociodemographic and maternal obstetric measures and revealed four distinct classes. Women belonging to low SES latent classes, despite obstetric measures, were more likely to have preterm birth and low birth weight. While these birth outcomes are often intertwined, our study revealed two high-risk classes. First, women characterized by co-occurring risks of low SES, early marriage, multigravida, and having more than one child were at an increased risk of preterm delivery. Thus, the combination of prior maternal obstetric measures and lower SES may need to be identified before pregnancy or early during pregnancy, monitored and treated for pregnancy complications and infections to prevent subsequent preterm deliveries. Secondly, women characterized by low SES, later marriage, primigravida, and no children were at an increased risk of delivering a low birth weight infant. Low SES women experiencing their first pregnancy may lack adequate resources and knowledge about maternal healthcare, which could increase the risk of a low birth weight infant.

Education and counseling to primigravida women with pragmatic recommendations by healthcare providers and midwives are paramount.

Overall, the co-occurring theme between these two classes is low SES, which remained as a major determinant of adverse birth outcomes in our studies and the literature. Thus, our studies suggest the need to identify evidence-based strategies, provide education and workforce development training, and allocate resources particularly to low SES groups to address the high burden of preterm birth and low birth weight. The SES disparities highlight an increasing need to promote educational attainment among rural young girls in India. The completion of secondary education has been associated with increased enrollment in higher education, paid employment, higher earnings in household income, access to government resources, healthy nutrition, medical compliance, and quality healthcare, ultimately improving the health and well-being of the women and their families. Furthermore, completion of secondary education may also delay early marriage, offer reproductive planning choices and prevent adolescent pregnancies. Additionally, family planning education programs can prevent unintended pregnancies and encourage optimal birth spacing to promote healthy birth outcomes. By educating young girls and women, they can be equipped with better decision-making skills for pregnancy and childbirth. While programs exist in India that tackle early marriage among girls and women in India, there have been marginal gains in the delay of marriage and completion of secondary education. Girls and women should be involved in the program design and implementation to promote cultural acceptability, appropriateness, and feasibility of such programs. Moreover, it is critically important to engage with community and religious leaders who can play a role in educating the girls and women. A comprehensive program evaluation is needed to quantify the impact of these programs. Moreover, qualitative methodologies are integral to assess the barriers, facilitators, and solutions in addressing early marriage and completion of secondary education. New evidence-based approaches that utilize implementation science methodology may be essential in closing the gap between proposed solutions and real-world solutions to increase programs efficacy and subsequently move to scaling up programs from the local level to the regional and national levels. The adoption of innovative solutions will be critical in reducing adverse birth outcomes.

Poverty remains a vital barrier that often forces young girls to opt out of completing secondary school, thus government funding is integral for low-income families to address poverty-related factors that prevent women from attaining further education. Further, increasing access to conditional cash transfers such as *Janani Suraksha Yojana (JSY)* is critical for families who are below the poverty line, because the uptake is not widespread (Randive et al. 2014). Barriers associated with this include the lack of awareness and knowledge of this government program as well as lack of proper documentation to be qualified for the program. ASHAs can play an integral role by informing and educating rural women of the qualifications, and assisting them in obtaining valid documentation, thus alleviating challenges faced by rural Indian women in accessing government funding. Additionally, programs that provide funding to pregnant women from conception to birth should be considered to improve birth outcomes. The JSY program is only awarded if certain conditions are met, which includes women giving birth in a facility, that can be a barrier in seeking funds and limits the potential benefit of the program. Therefore, programs and organizations have begun adopting the use of monthly unconditional cash transfers to elevate the women's access and availability of resources throughout the pregnancy (Brownell et al. 2018; Struthers et al. 2019). In India, the J Pal South Asia Program conducted a randomized controlled trial on the impact of unconditional cash transfers to pregnant women and lactating mothers on child health in Jharkhand, India (J-PAL South Asia 2021). The outcomes of this approach are still pending. Expanding existing programs and implementing new funding streams may be essential in reducing inequities among pregnant women.

In our second study, we examined the moderating role of the Accredited Social Health Activist (ASHA) program on the association between sociodemographic latent classes and preterm birth or low birth weight. The findings demonstrated that accompanying women to ANC by ASHA moderates the risk of preterm birth among women in low SES. Surprisingly, ASHA home visits did not moderate the relationship between low SES classes and preterm birth or low birth weight. While the ASHA program has been administered nationwide, the training provided to ASHA workers are dependent on state-specific resources and the dissimilarities in the training may lead to heterogeneity as well as inconsistencies in service delivery. It is critically important to evaluate our study in other states or nationwide to examine if this is a widespread problem or only within the Mysore district. Thus, we can adapt the lessons learned in other states with a successful ASHA program and implement context-specific recommendations.

Moreover, the Indian government may need to reassess the ASHA program by applying a health systems perspective given that it is the largest community health worker program worldwide with nearly 1 million ASHAs throughout the country(Scott, George, and Ved 2019b). Even though some evaluation studies on the ASHA program have been conducted in individual states, there has not been a nationwide evaluation since the launch of the program, more than a decade ago. Since the implementation of the program, ASHA has successfully led to increased institutional delivery, increased ANC visits, and increased skilled birth attendance. However, there have been some shortcomings including poor knowledge gaps, inadequacies in the training process, limited community engagement and lack of knowledge and awareness of the ASHA program. Therefore, a nationwide study is warranted to evaluate the training components as well as assess the specific benefits of providing ASHA home visits for pregnant women. This is integral in promoting quality-care and encouraging ANC visits among those who are socioeconomically disadvantaged to improve and promote optimal birth outcomes in rural settings.

Lastly, our final study examined the mediating role of anemia in the relationship between low SES and preterm birth or low birth weight. In the mediation analysis, there were significant direct effects in the relationship between socioeconomic disadvantage "low SES and early marriage" and low birth weight. However, anemia did not mediate the relationship between the low SES class and low birth weight. Surprisingly, anemia was not directly association with preterm birth and low birth weight, despite findings in previous studies and the high burden of anemia among pregnant women in rural India. This may be partially attributed to limitations of our study including the hemoglobin cut-off of <10 g/dl for moderate or severe anemia (World Health Organization 2011), having only one baseline measure of hemoglobin assessment taken any timepoint in pregnancy, and the lack of information about iron-folic acid supplementation. Further, there may be other mediators such as biomarkers and inflammatory markers such as c-reactive proteins and cytokines within the causal pathway of these birth outcomes. Therefore, there is an increasing need to regularly screen and utilize repeated measures of anemia biomarkers and include precise measures to clearly examine the mediating role of anemia in the relationship between socioeconomic disadvantage and preterm birth or low birth weight.

Given that there is an evidence-based link between anemia and poor birth outcomes observed in previous studies, there is a need to promote healthy nutrition for optimal fetal growth and development. Iron-rich foods such as leafy greens i.e., spinach, legumes, and groundnuts can be vital in increasing the amount of iron among pregnant women. The World Health Organization has also recommended the use of fortified foods with enriched micronutrients, as it can be distributed to a wider population without significantly changing food consumption habits in the community community(World Health Organization 2011a). Fortified foods may include corn-soya blend, biscuits, and vegetables enriched with vitamin A and iodized salt. Furthermore, iron-folic acid (IFA) supplementation are recommended to pregnant woman in India, even though uptake remains low. However, prior recommendations have shown the challenges to achieving high levels of coverage and adherence in order to effectively reduce anemia. Socio-cultural biases against the uptake of IFA i.e., lack of family support of IFA pill uptake, and misconceptions of negative adverse outcomes to the baby, have resulted in low uptake and poor adherence. Moreover, pregnant women have cited the low uptake due to forgetfulness, and the negative side effects associated with the IFA such as nausea and constipation.

Changing behaviors or cultural norms can be difficult and may take many years. Researchers should assess the utility of behavior change interventions such as group counseling, individual counseling, daily reminder messages through mobile messaging to encourage the uptake and adherence of the IFA supplements. Community engagement and collaboration is essential to ensure that the village residents are heard by encouraging local partnerships between researchers, ASHAs and community members. Community members can co-lead education and counseling events for pregnant women. There is also a need for nationwide training of healthcare providers and building programmatic capacity of the existing guidelines of IFA supplementation as well as alternative solutions to reduce anemia prevalence among Indian pregnant women. Further, researchers may need to incorporate qualitative research to understand the barriers and perceptions of IFA supplementation to address misconceptions and barriers to increase IFA uptake and mitigate the prevalence of anemia.

There were several limitations in this dissertation worth mentioning. First, and foremost, gestational age was based on the last menstrual period, and this measure may be inaccurate since there were no ultrasound clinical measures to ascertain. Secondly, anemia was not well-characterized given that there was only one baseline measure of hemoglobin assessment done at any timepoint during pregnancy. Thus, the findings would be more accurate with repeated measures of anemia since anemia can develop at any time during pregnancy. Lastly, this study was conducted in rural Mysore District, India, therefore there may be limited generalizability for urban districts in India. Nonetheless, this dissertation had several strengths. First, this study used a large sample in a rural setting and collected data prospectively. Second, employing LCA we examined co-occurring demographic and maternal factors in identifying high-risk women compared to assessing individual risk factors one at a time. Third, this study assessed the impact of the ASHA program, which is one of the largest community health worker programs, on preterm birth and low birth weight among high-risk women. Lastly, we assessed anemia, a prevalent and easily addressed condition as a mediator between one of the most consistent and significant predictors of poor birth outcomes, low SES, and preterm birth and low birth weight.

Overall, it remains critical to engage diverse stakeholders from education, government, and health sectors to promote sustainable approaches to address adverse neonatal outcomes. It is critical to develop cultural- and context-specific interventions to ensure that there is uptake of IFA supplementation. By implementing evidence-based interventions such as increasing education efforts, providing training and capacity building, allotting government funding, promoting healthy nutrition, and early screening for anemia biomarkers, we can reduce preterm birth and low birth weight outcomes in rural India.

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