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## Prevalence and Predictors of Preterm Births in Nepal- Findings from a prospective, population-based pregnancy cohort in rural Nepal: A secondary data analysis

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## ABSTRACT

### Objective

Preterm birth can have short and long-term complications for a child. Baseline socioeconomic factors and pregnancy-related signs and symptoms may be important to predict and prevent preterm births in low-resource settings. The objective of our study was to find prevalence and predictors of preterm birth in rural Nepal.

### Design

This is a secondary observational analysis of data.

### Setting

Rural Sarlahi district, Nepal

### Participants

40,119 pregnant women enrolled from September 9, 2010, to Jan 16, 2017

### Outcome Measures

The outcome variable is preterm birth. Generalized Estimating Equations (GEE) Poisson regression with robust variance was fitted to present effect estimates as risk ratios.

### Result

The prevalence of preterm birth was 15% (95% CI: 14.6%, 15.4%). Baseline characteristics associated with increased risk of preterm birth were maternal age less than 18 (ARR=1.13, 95% CI: 1.02-1.26); being Muslim (1.53, 1.16-2.01); first pregnancy (1.15, 1.04-1.28); multiple birth (4.91, 4.20-5.75) and male child (1.10, 1.02-1.17). Those associated with decreased risk were maternal education of more than 5 years (0.81, 0.73-0.90); and being from wealthier families (0.83, 0.74-0.93). Pregnancy related signs and symptoms associated with increased risk of preterm birth were vaginal bleeding (1.53, 1.08-2.18); swelling (1.37, 1.17-1.60); high systolic BP (1.47, 1.08-2.01) and high diastolic BP (1.41, 1.17-1.70) in the 3<sup>rd</sup> trimester. Those associated with decreased risk of preterm birth were respiratory problem in the 3<sup>rd</sup> trimester (0.86, 0.79-0.94); and having poor appetite, nausea and vomiting in the 2<sup>nd</sup> trimester (0.86, 0.80-0.92) and in the 3<sup>rd</sup> trimester (0.86, 0.79-0.94); and higher weight gain from the 2<sup>nd</sup> to 3<sup>rd</sup> trimester (0.89, 0.87-0.90).

### Conclusion

The prevalence of preterm is high in rural Nepal. Interventions that increase maternal education may play role. Monitoring morbidity during antenatal care to intervene to reduce them through an effective health system may help reduce preterm.

### Trial Registration Number

NCT01177111

### STRENGTHS AND LIMITATIONS OF THIS STUDY

- Previous studies on preterm birth in Nepal were hospital-based, enrolled women during delivery and have explored only the women's baseline socio-demographic factors associated with preterm birth. Our study is population-based, enrolls women from earlier days of pregnancy, and have explored symptoms and morbidity variables that change throughout pregnancy. Women were followed at monthly intervals to reduce recall bias about pregnancy symptoms and morbidities.
- Gestational age (GA) at outcome has been measured using date of last menstrual period (LMP), and not the standard ultrasound (USG) method, however, as LMP was asked at enrollment which was generally early in pregnancy, there is less recall bias than LMP recalled at delivery or late in pregnancy. In addition, the pregnancy surveillance, that asked women if they had their period in the past 5 weeks and administered a pregnancy test if not, have improved women's recall of date of LMP at the time of enrollment.

## INTRODUCTION:

Preterm birth (PTB), is defined as a birth occurring before 37 completed gestational weeks or fewer than 259 days from a woman's last menstrual period (LMP).[1] In 2010, the global prevalence of preterm birth estimated in 92 countries was 11.1% (95% CI: 9.1%-13.4%), ranging from about 5% in some European countries to 18% in some African countries.[2] Sixty percent of these PTBs occurred in Sub-Saharan Africa and South Asia.[2] Complications of preterm birth was the leading cause of under-5 mortality and accounted for approximately 17.7 % of all under-5 mortality and 36.1% of neonatal mortality, according to the 2019 global estimates. [3] Eighty-one percent of the under-5 deaths from complications of preterm birth occurred in Asia and sub-Saharan Africa countries.[4]

Preterm births can have short and long-term consequences. Short-term consequences comprise increased risks of neonatal respiratory conditions, sepsis, neurological conditions, feeding difficulties, and visual and hearing problems.[5-7] As the child grows, long term consequences include more hospital admissions, poorer neurodevelopment outcomes, difficulties in learning, as well as behavioral and social-emotional problems.[8-10] At the family level, preterm birth can lead to significant economic and psychological difficulties, and at the national level, it leads to significant cost for the health system.[11, 12]

In Nepal, under-five mortality has dropped from 64 deaths to 39 deaths per 1000 live births (LB) from 2001 to 2016.[13-15] In the same period, neonatal mortality has also steadily declined, (from 39 to 21 per 1,000 LB). [13-15]. Being an important determinant of neonatal mortality, preterm birth has become a greater contributor to under-5 mortality over time.[16] If we do not consider interventions to address preterm births, it would be difficult to achieve Nepal's Sustainable Development Goal (SDG) that aims to reduce the neonatal mortality to 12 per 1000 LB and under-5 mortality to 28 per 1000 LB by 2030.[17]

There are very few studies on the prevalence or risk factors for preterm birth in Nepal,[18, 19] and those that exist have limitations. First, most studies are hospital based. Women enrolled in hospitals during delivery may suffer from systematic recall bias, where women having a preterm birth might report differently from women with term births. Also, at the time of delivery, women might have recall issues in reporting their date of last menstrual period (LMP). Most important, enrolling at facilities has a selection bias, where the preterm births delivered



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3 at home or on-the-way to facilities are missed, possibly leading to underestimation of the  
4 prevalence and a different distribution of risk factors. Second, previous studies have included  
5 deliveries taken from urban tertiary hospitals in Nepal. Around 80% of the Nepalese population  
6 resides in rural areas[20] and do not have access to delivery services at tertiary centers. So, the  
7 findings from those studies may not be representative of rural Nepal. Third, since the women's  
8 enrollment was during delivery, they looked at only baseline risk factors and did not analyze  
9 changing symptoms and maternal weight gain throughout pregnancy. Some of these symptoms  
10 may be indicative of conditions that can be addressed by antenatal care. The objective of our  
11 study was to estimate the prevalence and identify predictors/risk factors of preterm births in  
12 rural Nepal. Understanding and addressing such risk factors is critical to addressing neonatal  
13 and child mortality and morbidity, particularly in resource-poor settings like Nepal.  
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## 23 **METHODS:**

### 24 **Study Design**

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26 This is a secondary data analysis with data taken from the Nepal Oil Massage Study (NOMS),  
27 which is a cluster-randomized community-based trial (ClinicalTrials.gov, NCT01177111) on  
28 the impact of sunflower seed oil versus standard of care mustard seed oil massage on neonatal  
29 mortality and morbidity in rural Sarlahi district of Nepal. This study began by identifying  
30 married women of childbearing age (15 to 40 years) who consented to pregnancy surveillance.  
31 This involved following them every 5 weeks to see whether they became pregnant, based on a  
32 positive pregnancy test offered by the study team if a woman reported missing a period. If  
33 pregnant, they were consented and enrolled in the trial. During enrollment, demographic data,  
34 socioeconomic status, reproductive history, and date of last menstruation were collected. Then  
35 they were visited monthly by a field worker until the pregnancy outcome occurred. During  
36 these monthly visits, field workers asked some basic questions about signs and symptoms of  
37 morbidity during the previous 30-day period. At these visits, women also had their weight and  
38 blood pressure (BP)/pulse measured, and body temperature recorded. Women reporting signs  
39 of morbidity and indicating that these signs were currently present were referred to the local  
40 health post or Primary Health Center. Women with fever or elevated blood pressure as  
41 measured by study staff were similarly referred.  
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58 As soon as possible after labor began or the baby was delivered, family members or neighbors  
59 notified the local female study worker of the birth. She notified a specially trained team who  
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3 visited the mother and infant as soon after birth as possible. They measured infant weight and  
4 time of weight measurement after birth, determined sex of the newborn and whether the baby  
5 was a singleton or multiple birth.  
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## 8 9 **Setting and Participants**

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12 The study cohort consists of 40,119 pregnancies among married women of child-bearing age,  
13 living in 34 VDCs of Sarlahi district, enrolled from September 9, 2010, to Jan 16, 2017, in the  
14 NOMS study. Pregnancies were followed monthly until delivery. Live births were categorized  
15 as term or preterm. Pregnancies ending in miscarriage, abortion and stillbirths (SB) were  
16 excluded from the analysis. Stillbirths were not included because the etiology of these may be  
17 quite different from those of preterm births.  
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## 23 24 **Variables**

### 25 26 Outcome Variable

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28 The main outcome variable is preterm birth among pregnancies that produced at least one live  
29 born infant, defined as pregnancies ending less than 259 gestational days from the first day of  
30 LMP date. Live births were based on women's self-report. They were asked if the baby moved,  
31 cried or breathed after birth. If they said "yes" to one or more of these, the birth was recorded  
32 as a live birth. For gestational age (GA), women were asked about their LMP during  
33 enrollment, and the GA at outcome was calculated as the difference between reported LMP  
34 and the date of the child's birth.  
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### 42 43 Independent Variables

44 Through literature review and expert opinion, certain factors were included in the analysis of  
45 predictors. [21] These can be categorized into baseline and pregnancy-varying variables.  
46 Baseline variables included sociodemographic, prior pregnancy related, current pregnancy  
47 related and child related variables. Pregnancy-varying variables included signs and symptoms  
48 of morbidity in pregnancy, and maternal weight.  
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54 Sociodemographic variables like maternal age, caste/religion, maternal education, wealth  
55 quintile and maternal height were explored. Maternal age was categorized as less than 18, 18-  
56 35 and more than 35 years to assess the association of very young women and older women  
57 with preterm births. Caste/religion of the mothers (Brahmin /Chhetri, Vaishya, Shudra, Muslim  
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3 and others) were used as per the caste category system in Nepal. [22] Maternal education (No  
4 schooling, 1-5 years and more than 5 years); and maternal height (<145 cm, 145-<150 and  
5 ≥150) were used. Household wealth status was measured in quintiles based on a standardized  
6 score using principal components analysis of household assets. [23]  
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12 Prior pregnancy related variables like parity (no prior pregnancy, prior pregnancy that did not  
13 result in a live or stillbirth, 1-4, and more than 4 prior pregnancies resulting in a live or stillbirth;  
14 interpregnancy interval (IPI) defined as the time since the end of last pregnancy to the date of  
15 LMP of the current pregnancy, regardless of the outcome (<18, 18-36, and >36 months); any  
16 prior live born child who died (Yes and No); any prior pregnancy that ended in a SB (Yes and  
17 No); any prior pregnancy that ended in multiples (Yes and No); and any prior pregnancy ending  
18 in miscarriage (Yes and No) were assessed.  
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26 Current pregnancy related variables like tobacco intake (ever used any tobacco products during  
27 this pregnancy- Yes and No), and alcohol intake (ever used alcohol during this pregnancy- Yes  
28 and No) were assessed. Child-level variables like multiple birth (singleton and twin/triplet),  
29 and sex of the child (male and female) were included. Current pregnancy related variables like  
30 tobacco and alcohol intake were not included in the regressions because rates of use were very  
31 low. Only 0.3% consumed alcohol and only 1.1% used tobacco. Other current pregnancy  
32 related variables like number of antenatal care (ANC) visits and place of delivery were shown  
33 in descriptive, but omitted from inferential analysis because in this setting, women with  
34 preterm births could have missed the 4th ANC visit in the 9<sup>th</sup> month and preterm birth could  
35 be the cause of a lower number of visits. For place of delivery, preterm births were more likely  
36 to be delivered at home or on the way to the facility, because many births in this environment  
37 are not planned to occur in a facility.  
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48 Symptoms of morbidity during pregnancy such as sexually transmitted diseases (STI),  
49 respiratory illness, gastrointestinal (GI) illness, poor appetite, nausea and vomiting, vaginal  
50 bleeding, swelling of hands or face, high systolic and diastolic blood pressure were assessed.  
51 All these variables were assessed in the 2<sup>nd</sup> and 3<sup>rd</sup> trimester, and so labelled as – Problem in  
52 at least one visit of the 2<sup>nd</sup> trimester- Yes or No, and Problem in at least one visit in the 3<sup>rd</sup>  
53 trimester- Yes or No. We did not include symptoms in the 1<sup>st</sup> trimester because only 41%  
54 women were enrolled in the 1<sup>st</sup> trimester, and so 59% missed symptom information in the 1<sup>st</sup>  
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3 trimester. Maternal weight gain was defined as the average weight in the 3<sup>rd</sup> trimester minus  
4 the average weight in the 2<sup>nd</sup> trimester. For measurement of these symptom variables, field  
5 workers asked if women had symptoms of morbidity at any time in the past 30 days, at each  
6 monthly visit during pregnancy. STI was defined as painful or burning urination, or foul  
7 smelling vaginal discharge. Respiratory illness was defined as persistent cough or difficult or  
8 rapid breathing, or wheezing/grunting, or shortness of breath. GI illness was defined as watery  
9 stools (4 or more times in a day or blood or white mucus in the stool). Appetite related illness  
10 was defined as poor appetite, nausea or vomiting. Vaginal bleeding was defined as spots of  
11 blood from the vagina. Swelling was defined as swelling of hands and/or face. Foot/leg  
12 swelling was excluded since it is common during pregnancy and not indicative of underlying  
13 disease. BP measurements were categorized as high systolic BP if the systolic measurement  
14 was  $\geq 140$  mmHg, and high diastolic BP if diastolic measurement was  $\geq 90$  mmHg at any  
15 monthly visit within the 2<sup>nd</sup> or 3<sup>rd</sup> trimester.  
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27 Preterm births were classified as spontaneous or not (caesarian section or induction), and only  
28 spontaneous preterm births were included in analysis.  
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### 31 32 **Statistical Methods**

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35 First, a descriptive analysis was done to show the frequencies of baseline variables (socio  
36 demographic, prior pregnancy related, current pregnancy and child related) and pregnancy  
37 varying variables (symptoms and maternal weight) by preterm and term births. Second,  
38 bivariable GEE Poisson regression with robust variance was used to examine associations  
39 between each risk factor and the outcome to get an unadjusted risk ratio. Since the prevalence  
40 of our outcome was more than 10%, we used Poisson regression with robust variance because  
41 we wanted to report associations as risk ratios. Third, multivariable GEE Poisson regression  
42 with robust variance was used including variables that were significant in the bivariable  
43 models, to get the adjusted risk ratios (ARR). Correlation between the different infants from  
44 the same mother was considered as exchangeable in the GEE model.  
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54 Among the 31,880 pregnancies that ended in a live birth, 29 pregnancies had missing  
55 gestational age at outcome. We excluded them from analysis, and so the descriptive analysis  
56 had 31,851 pregnancies. In the regression analysis, we excluded the pregnancies (3.4%) that  
57 ended in caesarian section, induction or both. Pregnancies with missing symptom variables  
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3 were further excluded. 59%, 20% and 9% pregnancies had symptom variables missing in the  
4 1<sup>st</sup>, 2<sup>nd</sup> and 3<sup>rd</sup> trimesters, respectively. We excluded first trimester data because data were  
5 missing for more than 50% pregnancies (women were not enrolled until after the 1<sup>st</sup> trimester).  
6 Since there was missing information for 29% of symptoms in 2<sup>nd</sup> and/or 3<sup>rd</sup> trimester, the final  
7 multivariable regression omitted these pregnancies, and so regression analysis consisted of  
8 21,297 pregnancies.  
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### 14 **Patient and Public Involvement**

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17 Patients or the public were not involved in the design, or conduct, or reporting, or  
18 dissemination plans of this study.  
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## 24 **RESULTS:**

### 25 **Participants**

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28 The analytic population is 31,851 pregnancies that ended in at least one live birth and had  
29 information on gestational age at outcome. The detailed flow chart is given in Figure 1. Most  
30 women were enrolled in the 1<sup>st</sup> and 2<sup>nd</sup> trimester (41% each), followed by the 3<sup>rd</sup> trimester  
31 (18%). Overall, the mean gestational age at enrollment was 18 weeks. For 1<sup>st</sup>, 2<sup>nd</sup> and 3<sup>rd</sup>  
32 trimesters, the mean GA at enrollment were 9, 19 and 34 weeks respectively.  
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### 40 **Descriptive Analysis**

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42 For baseline variables, as seen in Table 1, 15% of women were younger (less than 18) and 2%  
43 women were older (more than 35 years of age). 9% of women were Muslim caste/religion.  
44 Two thirds of women did not go to school, whereas only nearly one fourth had an education of  
45 more than five years. 15% of women had height <145cm. About a third (29%) of women had  
46 their first pregnancy in this study and 64% had one to four prior live or still births. Among  
47 those who had a previous pregnancy, 6% had prior still birth, 16% experienced miscarriage  
48 and 16% had a live birth that died, and only 1% had prior multiples. Half the women had an  
49 interpregnancy interval of less than 18 months, and 28% of women had four or more ANC  
50 visits. Half of the babies were born at home and 2% were born on the way to a facility or  
51 outdoors. Only 1.1% consumed tobacco and only 0.3% consumed alcohol during pregnancy.  
52 Half of the current pregnancies (51%) resulted in male children, and less than 1% resulted in  
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3 multiple births. Only 3.4% of pregnancies underwent either caesarian section or induction or  
4 both.  
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7 For pregnancy-varying variables, as seen in Table 2, poor appetite, nausea and vomiting was  
8 the most commonly reported symptom in both the second (39%) and third trimesters (20%);  
9 and vaginal bleeding was the least reported symptom (1.2% in the second and 0.6% in the third  
10 trimester). Very few women had high systolic blood pressure (0.5% and 0.8%) and high  
11 diastolic blood pressure (1.5% and 2.9%) in second and third trimesters respectively. The  
12 average weight gained by women from second to third trimester was 3.5 kg.  
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**Table 1: Distribution of Baseline Variables by preterm and term births**

| Variables  |                             | Total<br>N=31,851<br>N (%) | Term<br>N=27,059<br>N (%) | Preterm<br>N=4,792<br>N (%) |
|--|-----------------------------|----------------------------|---------------------------|-----------------------------|
| Maternal Age                                     | 18 to 35                    | 26,206 (82.3)              | 22,423 (82.9)             | 3,783 (78.9)                |
|  | Less than 18                | 4,946 (15.5)               | 4,100 (15.2)              | 846 (17.7)                  |
|  | More than 35                | 699 (2.2)                  | 536 (2.0)                 | 163 (3.4)                   |
| Caste/Religion                                   | Brahmin and Chhetri         | 963 (3.0)                  | 857 (3.2)                 | 106 (2.2)                   |
|  | Vaishya                     | 22,946 (72.0)              | 19,701 (72.8)             | 3,245 (67.7)                |
|  | Shudra                      | 4,922 (15.5)               | 4,111 (15.2)              | 811 (16.9)                  |
|  | Muslim and others           | 2,989 (9.4)                | 2,365 (8.7)               | 624 (13.0)                  |
|  | Missing                     | 31 (0.1)                   | 25 (0.1)                  | 6 (0.1)                     |
| Maternal Education                               | Missing                     | 21 (0.1)                   | 16 (0.1)                  | 5 (0.1)                     |
|  | No schooling                | 21,427 (67.3)              | 17,915 (66.2)             | 3,512 (73.3)                |
|  | 1 to 5 years                | 2,713 (8.5)                | 2,330 (8.6)               | 383 (8.0)                   |
|  | More than 5 years           | 7,681 (24.1)               | 6,786 (25.1)              | 895 (18.7)                  |
| Quintiles of Wealth                              | Missing                     | 30 (0.1)                   | 28 (0.1)                  | 2 (0.0)                     |
|  | Poorest                     | 6,510 (20.4)               | 5,340 (19.7)              | 1,170 (24.4)                |
|  | Poor                        | 6,380 (20.0)               | 5,403 (20.0)              | 977 (20.4)                  |
|  | Middle                      | 6,320 (19.8)               | 5,314 (19.6)              | 1,006 (21.0)                |
|  | Richer                      | 6,296 (19.8)               | 5,470 (20.2)              | 826 (17.2)                  |
|  | Richest                     | 6,324 (19.9)               | 5,516 (20.4)              | 808 (16.9)                  |
| Maternal Height (cms)                            | Missing                     | 21 (0.1)                   | 16 (0.1)                  | 5 (0.1)                     |
|  | <145                        | 4,689 (14.7)               | 3,885 (14.4)              | 800 (16.7)                  |
|  | 145-<150                    | 9,559 (29.9)               | 8,025 (29.7)              | 1,527 (31.9)                |
|  | >=150                       | 17,581 (55.1)              | 15,111 (55.8)             | 2,454 (51.2)                |
| Parity including both LB and SB, at Enrollment   | Missing                     | 51 (0.2)                   | 38 (0.14)                 | 11 (0.2)                    |
|  | Parity 1 to 4               | 20,317 (63.8)              | 17,366 (64.2)             | 2,951 (61.6)                |
|  | More than 4                 | 1,383 (4.3)                | 1,117 (4.1)               | 266 (5.6)                   |
|  | Prior Pregnant but parity 0 | 787 (2.5)                  | 672 (2.5)                 | 115 (2.4)                   |
|  | No Prior Pregnant           | 9,195 (28.9)               | 7,769 (28.7)              | 1,426 (29.8)                |
|  | Missing                     | 169 (0.5)                  | 135 (0.5)                 | 34 (0.7)                    |
| Interpregnancy Interval based on maternal recall | 18 to 36 months             | 7,927 (24.9)               | 6,787 (25.1)              | 1,140 (23.8)                |
|  | Less than 18 months         | 11,461 (36.0)              | 9,701 (35.9)              | 1,760 (36.7)                |
|  | More than 36 months         | 3,256 (10.2)               | 2,794 (10.3)              | 462 (9.6)                   |
|  | No Prior Pregnancy          | 9,195 (28.9)               | 7,769 (28.7)              | 1,426 (29.8)                |
|  | Missing                     | 12 (0.0)                   | 8 (0.0)                   | 4 (0.1)                     |
| Any deaths among Prior LB                        | Prior LB but not died       | 17,488 (54.9)              | 14,999 (55.4)             | 2,489 (51.9)                |
|  | Prior LB died               | 3,618 (11.4)               | 2,999 (11.1)              | 619 (12.9)                  |
|  | Prior Pregnancy but no LB   | 1,073 (3.4)                | 909 (3.4)                 | 164 (3.4)                   |
|  | No prior pregnancy          | 9,195 (28.9)               | 7,769 (28.7)              | 1,426 (29.8)                |
|  | Missing                     | 477 (1.5)                  | 383 (1.4)                 | 94 (2.0)                    |
|  | Prior Pregnancy but no SB   | 21,270 (66.8)              | 18,127 (67.0)             | 3,143 (65.6)                |
| Any prior pregnancy ended in SB                  | Prior SB                    | 1,371 (4.3)                | 1,150 (4.2)               | 221 (4.6)                   |

| Variables                                   |                                    | Total          | Term          | Preterm       |
|---|------------------------------------|----------------|---------------|---------------|
|   |                                    | N=31,851       | N=27,059      | N=4,792       |
|   |                                    | N (%)          | N (%)         | N (%)         |
| Any prior pregnancy ended in miscarriage    | No prior pregnancy                 | 9,195 (28.9)   | 7,769 (28.7)  | 1,426 (29.8)  |
|   | Missing                            | 15 (0.0)       | 13 (0.0)      | 2 (0.0)       |
|   | Prior Pregnancy but no miscarriage | 19,025 (59.7)  | 16,176 (59.8) | 2,849 (59.5)  |
|   | Prior miscarriage                  | 3,621 (11.4)   | 3,104 (11.5)  | 517 (10.8)    |
|   | No prior pregnancy                 | 9,195 (28.9)   | 7,769 (28.7)  | 1,426 (29.8)  |
| Any prior pregnancy ended in multiples      | Missing                            | 10 (0.0)       | 10 (0.0)      | 0 (0.0)       |
|   | Prior Pregnancy but no multiples   | 22,343 (70.1)  | 19,030 (70.3) | 3,313 (69.1)  |
|   | Prior multiples                    | 292 (0.9)      | 241 (0.9)     | 51 (1.1)      |
|   | No prior pregnancy                 | 9,195 (28.9)   | 7,769 (28.7)  | 1,426 (29.8)  |
|   | Missing                            | 21 (0.1)       | 19 (0.1)      | 2 (0.0)       |
| Number of ANC visits                        | No visit                           | 5,520 (17.3)   | 4,524 (16.7)  | 996 (20.8)    |
|   | 1 visit                            | 4,146 (13.0)   | 3,420 (12.6)  | 726 (15.2)    |
|   | 2-3 visit                          | 9,779 (30.7)   | 8,158 (30.1)  | 1,621 (33.8)  |
|   | 4 or more                          | 8,909 (28.0)   | 8,021 (29.6)  | 888 (18.5)    |
|   | Missing                            | 3,497 (11.0)   | 2,936 (10.9)  | 561 (11.7)    |
| Place of Delivery                           | Home/Maiti                         | 15,776 (49.5)  | 13,270 (49.0) | 2,506 (52.3)  |
|   | HP/Clinic/Hospital                 | 12,016 (37.7)  | 10,406 (38.5) | 1,610 (33.6)  |
|   | Way to Facility/Outdoors           | 610 (1.9)      | 486 (1.8)     | 124 (2.6)     |
|   | Missing                            | 3,449 (10.8)   | 2,897 (10.7)  | 552 (11.5)    |
|   | Bidi or tobacco use in pregnancy   | No             | 31,498 (98.9) | 26,789 (99.0) |
|   | Yes                                | 353 (1.1)      | 270 (1.0)     | 83 (1.7)      |
| Alcohol use (jaard or rakshi) in pregnancy? | No                                 | 31,756 (99.7)  | 26,982 (99.7) | 4,774 (99.6)  |
|   | Yes                                | 95 (0.3)       | 77 (0.3)      | 18 (0.4)      |
| Multiple Birth                              | Singleton                          | 31,587 (99.2)  | 26,946 (99.6) | 4,641 (96.8)  |
|   | Twin/Triplet                       | 264 (0.8)      | 113 (0.4)     | 151 (3.2)     |
| Sex of the child                            | Female                             | 15,182 (47.7)  | 13,063 (48.3) | 2,119 (44.2)  |
|   | Male                               | 16,306 (51.2)  | 13,794 (51.0) | 2,512 (52.4)  |
|   | Twin/Triplet                       | 264 (0.8)      | 113 (0.4)     | 151 (3.2)     |
|   | Missing                            | 99 (0.3)       | 89 (0.3)      | 10 (0.2)      |
|   | Induction or CS done               | Only Induction | 193 (0.6)     | 166 (0.6)     |
|   | Only CS                            | 868 (2.7)      | 735 (2.8)     | 133 (2.8)     |
|   | Both Induction and CS              | 32 (0.1)       | 28 (0.1)      | 4 (0.08)      |
|   | None                               | 30,758 (96.6)  | 26130 (96.6)  | 4628 (96.6)   |



**Table 2: Distribution of pregnancy-varying variables by preterm and term births**

| Variables  |         | Total<br>N=31,851<br>N (%) | Term<br>N=27,059<br>N (%) | Preterm<br>N=4,792<br>N (%) |
|--|---------|----------------------------|---------------------------|-----------------------------|
| STI in at least one visit of 2nd trimester?                              | No      | 20,823 (65.4)              | 17,497 (64.7)             | 3,326 (69.4)                |
|  | Yes     | 4,593 (14.4)               | 3,855 (14.2)              | 738 (15.4)                  |
|  | Missing | 6,435 (20.2)               | 5,707 (21.1)              | 728 (15.2)                  |
| STI in at least one visit of 3rd trimester?                              | No      | 25,931 (81.4)              | 22,512 (83.2)             | 3,419 (71.3)                |
|  | Yes     | 2,963 (9.3)                | 2,569 (9.5)               | 394 (8.2)                   |
|  | Missing | 2,957 (9.3)                | 1,978 (7.3)               | 979 (20.4)                  |
| Respiratory Problems in at least one visit of 2nd trimester?             | No      | 17,963 (56.4)              | 15,081 (55.7)             | 2,882 (60.1)                |
|  | Yes     | 7,452 (23.4)               | 6,271 (23.2)              | 1,181 (24.6)                |
|  | Missing | 6,436 (20.2)               | 5,707 (21.1)              | 729 (15.2)                  |
| Respiratory Problems in at least one visit of 3rd trimester?             | No      | 22,860 (71.8)              | 19,743 (73.0)             | 3,117 (65.0)                |
|  | Yes     | 6,034 (18.9)               | 5,338 (19.7)              | 696 (14.5)                  |
|  | Missing | 2,957 (9.3)                | 1,978 (7.3)               | 979 (20.4)                  |
| GI Problems in at least one visit of 2nd trimester?                      | No      | 22,742 (71.4)              | 19,136 (70.7)             | 3,606 (75.3)                |
|  | Yes     | 2,673 (8.4)                | 2,216 (8.2)               | 457 (9.5)                   |
|  | Missing | 6,436 (20.2)               | 5,707 (21.1)              | 729 (15.2)                  |
| GI Problems in at least one visit of 3rd trimester?                      | No      | 26,152 (82.1)              | 22,712 (83.9)             | 3,440 (71.8)                |
|  | Yes     | 2,742 (8.6)                | 2,369 (8.8)               | 373 (7.8)                   |
|  | Missing | 2,957 (9.3)                | 1,978 (7.3)               | 979 (20.4)                  |
| Poor app, nausea & vomiting in at least one visit of 2nd trimester?      | No      | 13,121 (41.2)              | 10,814 (40.0)             | 2,307 (48.1)                |
|  | Yes     | 12,295 (38.6)              | 10,538 (38.9)             | 1,757 (36.7)                |
|  | Missing | 6,435 (20.2)               | 5,707 (21.1)              | 728 (15.2)                  |
| Poor appetite, nausea & vomiting in at least one visit of 3rd trimester? | No      | 22,486 (70.6)              | 19,437 (71.8)             | 3,049 (63.6)                |
|  | Yes     | 6,409 (20.1)               | 5,645 (20.9)              | 764 (15.9)                  |
|  | Missing | 2,956 (9.3)                | 1,977 (7.3)               | 979 (20.4)                  |
| Vaginal Bleeding in at least one visit of 2nd trimester?                 | No      | 25,042 (78.6)              | 21,036 (77.7)             | 4,006 (83.6)                |
|  | Yes     | 373 (1.2)                  | 315 (1.2)                 | 58 (1.2)                    |
|  | Missing | 6,436 (20.2)               | 5,708 (21.1)              | 728 (15.2)                  |
| Vaginal Bleeding in at least one visit of 3rd trimester?                 | No      | 28,716 (90.2)              | 24,938 (92.2)             | 3,778 (78.8)                |
|  | Yes     | 178 (0.6)                  | 143 (0.5)                 | 35 (0.7)                    |
|  | Missing | 2,957 (9.3)                | 1,978 (7.3)               | 979 (20.4)                  |
| Swelling in at least one visit of 2nd trimester?                         | No      | 24,846 (78.0)              | 20,904 (77.3)             | 3,942 (82.3)                |
|  | Yes     | 571 (1.8)                  | 448 (1.7)                 | 123 (2.6)                   |
|  | Missing | 6,434 (20.2)               | 5,707 (21.1)              | 727 (15.2)                  |

| Variables  |                     | Total<br>N=31,851<br>N (%) | Term<br>N=27,059<br>N (%) | Preterm<br>N=4,792<br>N (%) |
|--|---------------------|----------------------------|---------------------------|-----------------------------|
| Swelling in at least one visit of 3rd trimester?                             | No                  | 27,754 (87.1)              | 24,126 (89.2)             | 3,628 (75.7)                |
|  | Yes                 | 1,141 (3.6)                | 956 (3.5)                 | 185 (3.9)                   |
|  | Missing             | 2,956 (9.3)                | 1,977 (7.3)               | 979 (20.4)                  |
| High Systolic BP in 2nd trimester?   | Normal Systolic BP  | 25,260 (79.3)              | 21,217 (78.4)             | 4,043 (84.4)                |
|  | High Systolic BP    | 158 (0.5)                  | 136 (0.5)                 | 22 (0.5)                    |
|  | Missing             | 6,433 (20.2)               | 5,706 (21.1)              | 727 (15.2)                  |
|  | Normal Systolic BP  | 28,659 (90.0)              | 24,905 (92.0)             | 3,754 (78.3)                |
| High Systolic BP in 3rd trimester?   | Normal Systolic BP  | 28,659 (90.0)              | 24,905 (92.0)             | 3,754 (78.3)                |
|  | High Systolic BP    | 241 (0.8)                  | 181 (0.7)                 | 60 (1.3)                    |
|  | Missing             | 2,951 (9.3)                | 1,973 (7.3)               | 978 (20.4)                  |
|  | Normal diastolic BP | 24,945 (78.3)              | 20,976 (77.5)             | 3,969 (82.8)                |
| High diastolic BP in 2nd trimester?  | Normal diastolic BP | 24,945 (78.3)              | 20,976 (77.5)             | 3,969 (82.8)                |
|  | High diastolic BP   | 473 (1.5)                  | 377 (1.4)                 | 96 (2.0)                    |
|  | Missing             | 6,433 (20.2)               | 5,706 (21.1)              | 727 (15.2)                  |
|  | Normal diastolic BP | 27,982 (87.9)              | 24,360 (90.0)             | 3,622 (75.6)                |
| High diastolic BP in 3rd trimester?  | Normal diastolic BP | 27,982 (87.9)              | 24,360 (90.0)             | 3,622 (75.6)                |
|  | High diastolic BP   | 918 (2.9)                  | 726 (2.7)                 | 192 (4.0)                   |
|  | Missing             | 2,951 (9.3)                | 1,973 (7.3)               | 978 (20.4)                  |
| Average weight in 3rd trimester minus Average weight in 2nd trimester (Mean) |                     | 3.5                        | 3.6                       | 2.9                         |

## Outcome data

There were 4,792 preterm births out of 31,851 pregnancies with at least one LB. Hence, the prevalence of preterm birth was 15% (95% CI: 14.6%, 15.4%) among the pregnancies enrolled between September 9, 2010, to January 16, 2017. On looking at severity of preterm, the prevalence were 0.5%, 1.5% and 2.1% and 10.9% for extreme PTB (<28 weeks), very PTB (28-<32 weeks), moderate PTB (32-<34 weeks) and late PTB (34-<37 weeks) respectively.

## Main results

The main results are shown in Table 3. Baseline variables that increased the risk of preterm were maternal age less than 18 (ARR=1.13, 95% CI: 1.02-1.26); being Muslim compared to Brahmin and Chhetri (1.53, 1.16-2.01); first pregnancy as compared to parity 1 to 4 (1.15, 1.04-1.28); having a multiple birth (4.91, 4.20-5.75) and having a male child (1.10, 1.02-1.17). Baseline variables that decreased the risk of preterm were maternal education of more than 5 years (0.81, 0.73-0.90); and being wealthier: richer (0.83, 0.74-0.93) wealth quintile compared to the poorest wealth quintile. Baseline variables that showed no association with preterm births in the bivariable/unadjusted models are any prior pregnancy ending in SB, any prior pregnancy ending in multiples, and any prior pregnancy ending in miscarriage, and interpregnancy interval. The baseline variable that showed an association in the bivariable model, but not in the multivariable models was any prior pregnancy ending in death for a live birth.

For morbidity symptoms, some increased the risk of preterm, and all of these showed increased risk when symptoms were present in the 3<sup>rd</sup> trimester. Having vaginal bleeding (ARR= 1.53, 95% CI: 1.08-2.18); swelling (1.37, 1.17-1.60); high systolic BP (1.47, 1.08-2.01) and high diastolic BP (1.41, 1.17-1.70) in the 3<sup>rd</sup> trimester significantly increased the risk of preterm. Some symptom variables significantly decreased the risk of preterm. Having respiratory problem in the 3<sup>rd</sup> trimester (0.86, 0.79-0.94); and having poor appetite, nausea and vomiting in the 2<sup>nd</sup> trimester (0.86, 0.80-0.92) and in the 3<sup>rd</sup> trimester (0.86, 0.79-0.94) decreased the risk of preterm. Symptom variables that showed no association with preterm were STI and GI problems. Symptom variables that were significant in the bivariable model, but not significant in the multivariable models were swelling in the 2<sup>nd</sup> trimester and diastolic blood pressure in the 2<sup>nd</sup> trimester. For maternal weight, higher weight gain from the 2<sup>nd</sup> to the 3<sup>rd</sup> trimester was associated with a decreased the risk of preterm (0.89, 0.87-0.90).

**Table 3: Crude and Adjusted Risk Ratios for associations between risk factors and preterm birth**

| Name of Variables                              | Categories                         | Unadjusted Model<br>Risk Ratio (95% CI) | Adjusted Model<br>(N=21,297)<br>Risk Ratio (95% CI) |
|--|------------------------------------|---|---|
| Maternal Age                                   | 18 to 35                           | 1                                       | 1   |
|  | Less than 18                       | 1.19*** [1.11,1.28]                     | 1.13* [1.02,1.26]                                   |
|  | More than 35                       | 1.57*** [1.36,1.81]                     | 1.22 [0.98,1.51]                                    |
| Caste/Religion Categories                      | Brahmin and Chhetri                | 1                                       | 1   |
|  | Vaishya                            | 1.33** [1.09,1.62]                      | 1.23 [0.95,1.59]                                    |
|  | Shudra                             | 1.55*** [1.26,1.90]                     | 1.23 [0.94,1.62]                                    |
|  | Muslim and others                  | 1.96*** [1.60,2.42]                     | 1.53** [1.16,2.01]                                  |
| Mother's Years of Education                    | No schooling                       | 1                                       | 1   |
|  | 1 to 5 years                       | 0.86** [0.78,0.95]                      | 0.91 [0.80,1.03]                                    |
|  | More than 5 years                  | 0.71*** [0.66,0.76]                     | 0.81*** [0.73,0.90]                                 |
| 5 quintiles of Wealth                          | Poorest                            | 1                                       | 1   |
|  | Poor                               | 0.86*** [0.79,0.93]                     | 0.90* [0.82,1.00]                                   |
|  | Middle                             | 0.89** [0.82,0.96]                      | 0.95 [0.86,1.05]                                    |
|  | Richer                             | 0.73*** [0.67,0.79]                     | 0.83** [0.74,0.93]                                  |
|  | Richest                            | 0.71*** [0.65,0.77]                     | 0.88* [0.78,1.00]                                   |
| Mother's height(centimeter)                    | <145                               | 1                                       | 1   |
|  | 145-<150                           | 0.93 [0.86,1.01]                        | 0.98 [0.88,1.08]                                    |
|  | >=150                              | 0.81*** [0.75,0.87]                     | 0.89* [0.81,0.98]                                   |
| Parity including both LB and SB, at Enrollment | Parity 1 to 4                      | 1                                       | 1   |
|  | More than 4                        | 1.32*** [1.17,1.48]                     | 1.17 [0.99,1.37]                                    |
|  | Prior Pregnant but parity 0        | 1.02 [0.85,1.22]                        | 0.92 [0.62,1.37]                                    |
|  | No Prior Pregnant                  | 1.10** [1.04,1.17]                      | 1.15** [1.04,1.28]                                  |
| Interpregnancy Intervals                       | 18 to 36 months                    | 1                                       | 1   |
|  | Less than 18 months                | 1.07 [0.99,1.14]                        | 1.08 [0.99,1.18]                                    |
|  | More than 36 months                | 0.98 [0.89,1.09]                        | 0.9 [0.79,1.02]                                     |
|  | No Prior Pregnancy                 | 1.11** [1.03,1.20]                      | 1 [1.00,1.00]                                       |
| Any prior pregnancy ended in death for LB?     | Prior LB but not died              | 1                                       | 1   |
|  | Prior LB died                      | 1.19*** [1.09,1.29]                     | 1.07 [0.97,1.19]                                    |
|  | Prior Pregnancy but no LB          | 1.07 [0.92,1.25]                        | 1.06 [0.75,1.49]                                    |
|  | No prior pregnancy                 | 1.12*** [1.06,1.19]                     | 1 [1.00,1.00]                                       |
| Any prior pregnancy ended in SB?               | Prior Pregnancy but no SB          | 1                                       | 1   |
|  | Prior SB                           | 1.08 [0.94,1.23]                        | 1.08** [1.02,1.15]                                  |
|  | No Prior Pregnancy                 | 1.08** [1.02,1.15]                      | 1.08** [1.02,1.15]                                  |
| Any prior pregnancy ended in miscarriage?      | Prior Pregnancy but no miscarriage | 1                                       | 1   |
|  | Prior miscarriage                  | 0.94 [0.86,1.03]                        | 1.07* [1.01,1.13]                                   |
|  | No Prior Pregnancy                 | 1.07* [1.01,1.13]                       | 1.07* [1.01,1.13]                                   |
| Any prior pregnancy ended in multiples?        | Prior Pregnancy but no multiples   | 1                                       | 1   |
|  | Prior multiples                    | 1.14 [0.87,1.49]                        | 1.08** [1.02,1.14]                                  |
|  | No prior pregnancy                 | 1.08** [1.02,1.14]                      | 1.08** [1.02,1.14]                                  |
| Multiple Birth                                 | Singleton                          | 1                                       | 1   |
|  | Twin/Triplet                       | 3.92*** [3.52,4.38]                     | 4.91*** [4.20,5.75]                                 |
| Sex of the child                               | Female                             | 1                                       | 1   |
|  | Male                               | 1.10*** [1.04,1.17]                     | 1.10** [1.02,1.17]                                  |

| Name of Variables  | Categories          | Unadjusted Model<br>Risk Ratio (95% CI) | Adjusted Model<br>(N=21,297)<br>Risk Ratio (95% CI) |
|--|---------------------|---|---|
|  | Twin/Triplet        | 4.13*** [3.69,4.63]                     | 1   |
| STI in at least one visit of 2nd trimester?                              | No                  | 1                                       |   |
|  | Yes                 | 0.99 [0.92,1.07]                        |   |
| STI in at least one visit of 3rd trimester?                              | No                  | 1                                       |   |
|  | Yes                 | 1.01 [0.92,1.12]                        |   |
| Respiratory Problems in at least one visit of 2nd trimester?             | No                  | 1                                       | 1   |
|  | Yes                 | 1 [0.94,1.06]                           | 1.08 [1.00,1.16]                                    |
| Respiratory Problems in at least one visit of 3rd trimester?             | No                  | 1                                       | 1   |
|  | Yes                 | 0.85*** [0.79,0.92]                     | 0.86** [0.79,0.94]                                  |
| GI Problems in at least one visit of 2nd trimester?                      | No                  | 1                                       |   |
|  | Yes                 | 1.08 [0.98,1.18]                        |   |
| GI Problems in at least one visit of 3rd trimester?                      | No                  | 1                                       |   |
|  | Yes                 | 1.04 [0.94,1.16]                        |   |
| Poor app, nausea & vomiting in at least one visit of 2nd trimester?      | No                  | 1                                       | 1   |
|  | Yes                 | 0.81*** [0.77,0.86]                     | 0.86*** [0.80,0.92]                                 |
| Poor appetite, nausea & vomiting in at least one visit of 3rd trimester? | No                  | 1                                       | 1   |
|  | Yes                 | 0.88** [0.82,0.95]                      | 0.86*** [0.79,0.94]                                 |
| Vaginal Bleeding in at least one visit of 2nd trimester?                 | No                  | 1                                       | 1   |
|  | Yes                 | 0.91 [0.71,1.17]                        | 0.84 [0.71,1.17]                                    |
| Vaginal Bleeding in at least one visit of 3rd trimester?                 | No                  | 1                                       | 1   |
|  | Yes                 | 1.44* [1.05,1.98]                       | 1.53* [1.08,2.18]                                   |
| Swelling in at least one visit of 2nd trimester?                         | No                  | 1                                       | 1   |
|  | Yes                 | 1.32*** [1.12,1.55]                     | 1.19 [0.98,1.46]                                    |
| Swelling in at least one visit of 3rd trimester?                         | No                  | 1                                       | 1   |
|  | Yes                 | 1.25** [1.09,1.44]                      | 1.37*** [1.17,1.60]                                 |
| High Systolic BP in 2nd trimester?                                       | Normal Systolic BP  | 1                                       | 1   |
|  | High Systolic BP    | 0.89 [0.59,1.34]                        | 0.67 [0.40,1.12]                                    |
| High Systolic BP in 3rd trimester?                                       | Normal Systolic BP  | 1                                       | 1   |
|  | High Systolic BP    | 1.92*** [1.52,2.41]                     | 1.47* [1.08,2.01]                                   |
| High diastolic BP in 2nd trimester?                                      | Normal diastolic BP | 1                                       | 1   |
|  | High diastolic BP   | 1.34** [1.12,1.60]                      | 1.09 [0.85,1.40]                                    |
| High diastolic BP in 3rd trimester?                                      | Normal diastolic BP | 1                                       | 1   |
|  | High diastolic BP   | 1.57*** [1.37,1.80]                     | 1.41*** [1.17,1.70]                                 |
| Average weight in 3rd trimester minus Average weight in 2nd trimester    |                     | 0.88*** [0.87,0.90]                     | 0.89*** [0.87,0.90]                                 |

\*  $p < 0.05$ , \*\*  $p < 0.01$ , \*\*\*  $p < 0.001$

## DISCUSSION

Our study is one of the only large-scale studies on preterm births using data from an existing pregnancy surveillance in rural Sarlahi, Nepal. The prevalence of preterm birth is 15%, higher than previous estimates from Nepal [18, 19] which were primarily from urban areas and large hospital-based studies. Our study's strength is that it was population-based and included all home and facility deliveries but is confined to a rural and relatively small geographic area (one third of a district). It should also be noted that health care seeking in pregnancy is low considering the low rates of antenatal care and facility deliveries. The low rates of induction and caesarean section point to a very low proportion of the PTBs being due to iatrogenic causes.

In many other settings, both younger and older maternal age has been reported to be risk factors for preterm birth. [24-30]. First pregnancy (primipara) has been shown to be associated with preterm birth in other studies. A study in France showed that primipara as compared to parity 2-3 increased the risk of preterm birth by 1.8 times.[31] Another study in the USA showed that being primipara as compared to multipara increased the risk of very preterm and extremely preterm birth, with the highest risk of 1.37 times for extremely preterm birth.[32] Primipara is a risk factor for hypertensive disorders of pregnancy (HDP), which increases the risk of preterm birth.[33] Our study did not show interpregnancy interval to be the risk factor for preterm birth. However, other studies on relationships between interpregnancy interval and preterm birth consistently showed that shorter interpregnancy intervals increase the risk of preterm births. However, the intervals used were not uniform across studies. One study found that, compared to an IPI of 18–23 months, IPIs <3, 3–5, and 6–12 months had higher risks for preterm birth.[34] Another study with median IPI of 36 months showed that, compared to an IPI of 24–36 months, an IPI of <24 months was associated with preterm delivery.[35] Different studies corroborate our finding that multiple births are a risk factor for preterm birth. [18, 36, 37] Similar to our study, others also found male children at higher risk of being preterm[38-40], but a study in Nepal found that female children had a higher risk of being preterm.[18] This study in Nepal enrolled live births in a hospital setting, and had almost half the prevalence of our study. [18] They could have missed more males that had preterm births at home or on the way to a facility.

Different studies in Nepal [18] and outside of Nepal [41-43] have also shown that higher education of mothers decreases the risk of preterm births. Higher education of mothers can lead

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3 to increased knowledge and awareness regarding pregnancy-related care and thus decrease  
4 adverse outcomes of pregnancy. We found that women in the richer wealth quintile had a lower  
5 risk of preterm births. Having higher household economic status probably does not directly  
6 affect the gestational age at outcome, instead, it probably is mediated by factors like nutrition,  
7 physically demanding work during pregnancy, type of care at home, stress level and other  
8 psychological factors.[44]  
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15 Pregnancy-varying morbidities that significantly decreased the risk of preterm birth in our  
16 analysis were respiratory problems in the 3<sup>rd</sup> trimester; and poor appetite, nausea and vomiting  
17 in the 2<sup>nd</sup> trimester, and the 3<sup>rd</sup> trimester. The association found with respiratory problems is  
18 not clear, as we did not find any studies showing this association in the literature. A study by  
19 Wallin et. al. in Nepal showed similar findings - poor appetite, nausea and vomiting in first  
20 trimester was not significantly associated with preterm births, but having these symptoms in  
21 the 2<sup>nd</sup> trimester decreased the risk of preterm by 25%.[45]  
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29 Pregnancy-varying morbidities that significantly increased the risk of preterm were vaginal  
30 bleeding, swelling of hands and face, high diastolic and systolic BP, all in the 3<sup>rd</sup> trimester.  
31 Other studies show similar results for vaginal bleeding. Vaginal bleeding is associated with  
32 fetal exposure to oral pathogens, which thereby increases the risk of preterm birth, however,  
33 whether bleeding is the cause or result of fetal exposure to oral pathogens is not clear.[46] A  
34 prospective cohort study in the US, separating first and second trimesters showed that vaginal  
35 bleeding in both trimesters increased the risk of preterm birth by 3.6 times, while bleeding in  
36 the second trimester only, was not associated with preterm birth.[47] A systematic review using  
37 23 studies showed that bleeding in early pregnancy increased the risk of preterm births.[48] A  
38 study in China showed that vaginal bleeding in the first-trimester increased the risk of preterm  
39 births, and the severity, duration and initial timing of vaginal bleeding had different effects on  
40 the severity of preterm births.[46] Due to the low enrollment of women in the 1<sup>st</sup> trimester, we  
41 could not look at the association of vaginal bleeding in the 1<sup>st</sup> trimester with preterm birth.  
42 However, all of the above information indicates that vaginal bleeding can be an important  
43 predictor of preterm birth and health care workers should recommend appropriate interventions  
44 for women if they present with vaginal bleeding (such as more frequent follow up or referral  
45 for higher level care).  
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3 Other studies on blood pressure during pregnancy have also shown that a rise in systolic BP  
4 (over 30 mm Hg) or diastolic BP (over 15mm Hg), from early pregnancy to the mid third  
5 trimester significantly increased the risk of spontaneous preterm birth by 2 to 3 times.[49]  
6  
7 Another study showed that an increase in 10 mm Hg in diastolic BP increased the risk of  
8 preterm birth by 29%. [50] These indicate the importance of measuring BP during the 3<sup>rd</sup>  
9 trimester. High BP in the 3<sup>rd</sup> trimester is an indicator of pre-eclampsia/eclampsia and can  
10 predict preterm birth. Measuring BP frequently and monitoring the rise and cause of increased  
11 BP is important for predicting preterm birth.  
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19 For maternal weight, higher weight gain from the 2<sup>nd</sup> to the 3<sup>rd</sup> trimester decreased the risk of  
20 preterm. This is consistent with a study done outside Nepal, which showed that very low weight  
21 gain was strongly associated with very preterm delivery, and that this varied by pre-pregnancy  
22 BMI, where underweight women had the highest association and very obese women had lowest  
23 association with preterm.[51] Since our study is in a non-obese population, less maternal  
24 weight gain can pose a risk to preterm births. Given preterm births have shorter gestation, the  
25 increase in weight gain will likely be less because there is less time to increase weight,  
26 especially in the third trimester, when much of the gestational weight it gained.  
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### 34 **Strengths and Limitations**

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36 In this study, GA at outcome has been measured using date of LMP, and not the standard  
37 ultrasound (USG) method. However, as LMP was asked at enrollment which was generally  
38 early in pregnancy, there is less recall bias than LMP recalled at delivery or late in pregnancy.  
39 In addition, the pregnancy surveillance, that asked women if they had their period in the past 5  
40 weeks and administered a pregnancy test if not, may have improved women's recall of date of  
41 LMP at the time of enrollment. Women were followed prospectively at monthly intervals to  
42 reduce recall bias about pregnancy morbidities and symptoms. In order to reduce  
43 misclassification of stillbirths and live births, women were asked whether the infant moved,  
44 breathed or cried after birth.  
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54 Some variables associated with increased risk of preterm births in previous studies, like a prior  
55 pregnancy ending in a preterm birth, gestational diabetes and maternal anemia could not be  
56 included in this analysis because they were not measured in the main trial. However, other  
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3 important morbidity variables have been measured and used in the analysis. These risk factors  
4 are likely generalizable for similar populations in South Asia.  
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## 8 9 **CONCLUSION**

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11 Preterm birth is a leading risk factor for neonatal and under-5 mortality and morbidity  
12 worldwide. To reduce neonatal mortality, preventing preterm births can be a vital step. Some  
13 of the risk factors from our study are amenable to antenatal interventions but many others need  
14 more understanding of the underlying causal mechanisms. Maternal education and awareness  
15 can play a role in the long term, while good quality antenatal care, as suggested by the new  
16 WHO recommendation of 8 contacts during pregnancy, may help reduce some PTBs. Future  
17 research should focus on basic research involving the field of ‘omics’ using biological samples  
18 and implementation research to improve antenatal care and maternal nutrition.  
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## 26 27 **OTHER INFORMATION**

### 28 29 **Ethics approval and consent to participate**

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31 NOMS was approved by the institutional review board (IRB) of the Johns Hopkins Bloomberg  
32 School of Public Health in the USA and by the IRB of the Institute of Medicine, Tribhuvan  
33 University, Kathmandu, Nepal. This analysis of secondary data was considered exempt by the  
34 Johns Hopkins Bloomberg School of Public Health institutional review board (IRB)  
35 (FWA00000287). Verbal consent was obtained from women for their participation and their  
36 infants for the primary data collection.  
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### 44 45 **Consent for publication:**

46  
47 No individual information including data, images and video are included in this manuscript.  
48  
49

### 50 51 **Availability of data and materials:**

52  
53 No data are available.  
54  
55

### 56 57 **Competing interests:**

58  
59 The authors declare that they have no competing interests.  
60

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**Authors' contribution:**

SS, EH, DM, SZ, REB and JK conceptualized and designed the analysis. SS conducted the analysis and wrote the manuscript. LCM, JMT, SKK, SLC and JK were investigators in the parent trial. All authors reviewed results, analysis, discussed interpretations, and contributed to development and revision of the manuscript.

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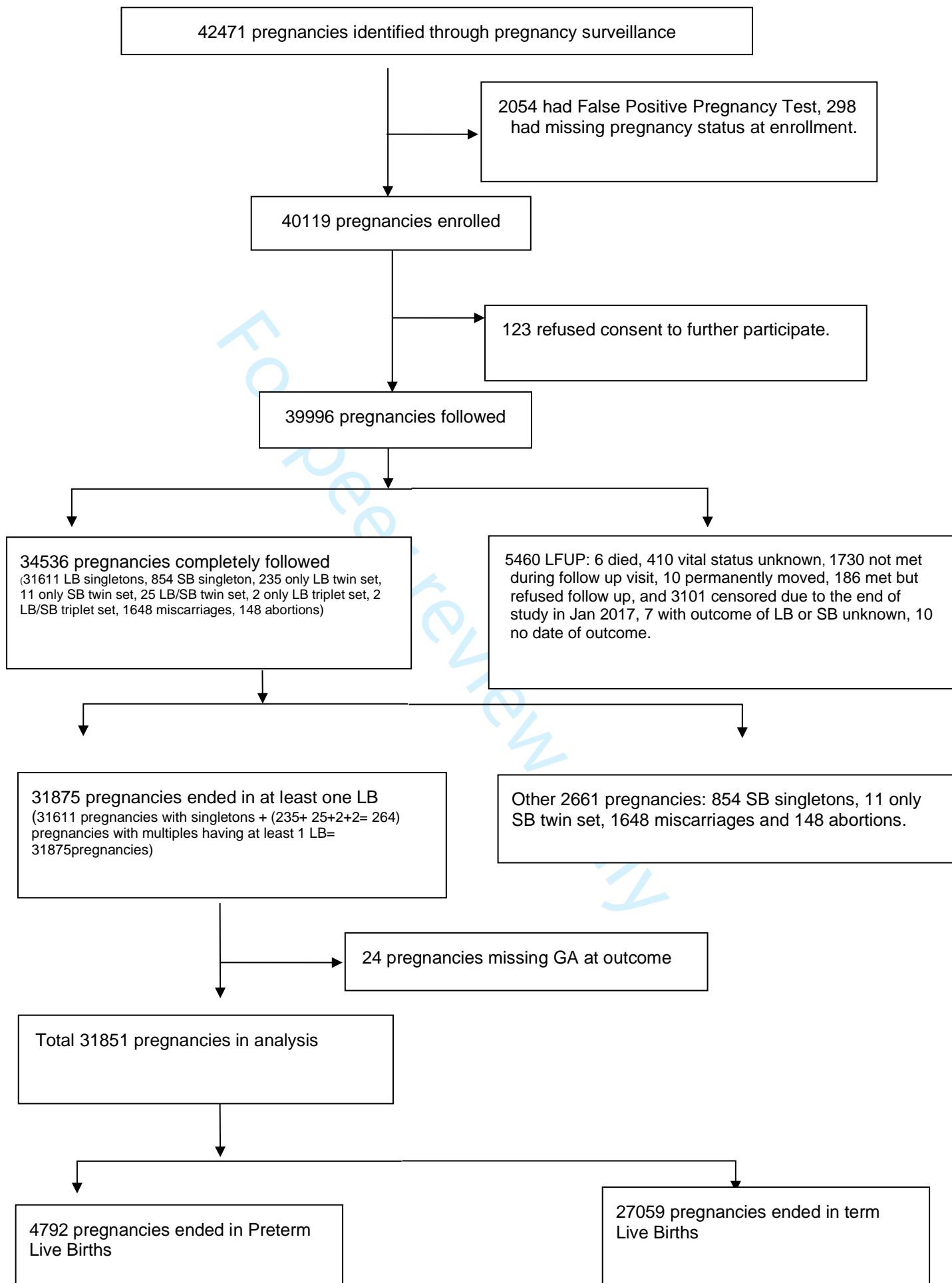
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**Figure 1: Flow Diagram for Participants**

# BMJ Open

## Prevalence and Predictors of Spontaneous Preterm Births in Nepal- Findings from a prospective, population-based pregnancy cohort in rural Nepal: A secondary data analysis

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3 **Prevalence and Predictors of Spontaneous Preterm Births in Nepal- Findings from a**  
4 **prospective, population-based pregnancy cohort in rural Nepal: A secondary data**  
5 **analysis**  
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## ABSTRACT

### Objective

Preterm birth can have short and long-term complications for a child. Socioeconomic factors and pregnancy-related morbidities may be important to predict and prevent preterm births in low-resource settings. The objective of our study was to find prevalence and predictors of spontaneous preterm birth in rural Nepal.

### Design

This is a secondary observational analysis of trial data (registration number NCT01177111)

### Setting

Rural Sarlahi district, Nepal

### Participants

40,119 pregnant women enrolled from September 9, 2010, to Jan 16, 2017

### Outcome Measures

The outcome variable is spontaneous preterm birth. Generalized Estimating Equations (GEE) Poisson regression with robust variance was fitted to present effect estimates as risk ratios.

### Result

The prevalence of spontaneous preterm birth was 14.5% (0.5% non-spontaneous). Characteristics not varying in pregnancy associated with increased risk of preterm birth were maternal age less than 18 (ARR=1.13, 95% CI: 1.02-1.26); being Muslim (1.53, 1.16-2.01); first pregnancy (1.15, 1.04-1.28); multiple birth (4.91, 4.20-5.75) and male child (1.10, 1.02-1.17). Those associated with decreased risk were maternal education >5 years (0.81, 0.73-0.90); maternal height  $\geq 150$  cm (0.89, 0.81-0.98) and being from wealthier families (0.83, 0.74-0.93). Pregnancy related morbidities associated with increased risk of preterm birth were vaginal bleeding (1.53, 1.08-2.18); swelling (1.37, 1.17-1.60); high systolic BP (1.47, 1.08-2.01) and high diastolic BP (1.41, 1.17-1.70) in the 3<sup>rd</sup> trimester. Those associated with decreased risk were respiratory problem in the 3<sup>rd</sup> trimester (0.86, 0.79-0.94); and having poor appetite, nausea and vomiting in 2<sup>nd</sup> trimester (0.86, 0.80-0.92) and 3<sup>rd</sup> trimester (0.86, 0.79-0.94); and higher weight gain from 2<sup>nd</sup> to 3<sup>rd</sup> trimester (0.89, 0.87-0.90).

### Conclusion

The prevalence of preterm is high in rural Nepal. Interventions that increase maternal education may play a role. Monitoring morbidities during antenatal care to intervene to reduce them through an effective health system may help reduce preterm.

## STRENGTHS AND LIMITATIONS OF THIS STUDY

- This is a large population-based study that allows for analysis of rare and common risk factors for a relatively rare outcome (preterm).
- Previous studies on preterm birth in Nepal were hospital-based, enrolled women during delivery and have explored only the women's socio-demographic factors associated with preterm birth, whereas our study is population-based, enrolls women from earlier in pregnancy, follows them monthly, and has explored symptoms and morbidities variables that change through pregnancy.
- Gestational age (GA) at outcome has been measured using date of last menstrual period (LMP) as usually done in LMICs, however, as LMP was asked at enrollment that was generally early in pregnancy, there is less recall bias than LMP recalled at delivery or late in pregnancy.
- Missing data for second trimester morbidities due to late enrollment of some women in pregnancy is a limitation, but comparison of sociodemographic characteristics suggest limited potential for biases due to this limitation.

## INTRODUCTION:

Preterm birth (PTB) is defined as a birth occurring before 37 completed gestational weeks or fewer than 259 days from a woman's last menstrual period (LMP).[1] In 2010, the global prevalence of preterm birth estimated in 92 countries was 11.1% (95% CI: 9.1%-13.4%), ranging from about 5% in some European countries to 18% in some African countries.[2] Sixty percent of these PTBs occurred in Sub-Saharan Africa and South Asia.[2] Complications of preterm birth was the leading cause of under-5 mortality and accounted for approximately 17.7 % of all under-5 mortality and 36.1% of neonatal mortality, according to the 2019 global estimates. [3] Eighty-one percent of the under-5 deaths from complications of preterm birth occurred in Asia and sub-Saharan Africa countries.[4]

Preterm births can have short and long-term consequences. Short-term consequences comprise increased risks of neonatal respiratory conditions, sepsis, neurological conditions, feeding difficulties, and visual and hearing problems.[5-7] As the child grows, long term consequences include more hospital admissions, poorer neurodevelopment outcomes, difficulties in learning, as well as behavioral and social-emotional problems.[8-10] At the family level, preterm birth can lead to significant economic and psychological difficulties, and at the national level, it leads to significant cost for the health system.[11, 12]

In Nepal, under-five mortality has dropped from 64 deaths to 39 deaths per 1000 live births (LB) from 2001 to 2016.[13-15] In the same period, neonatal mortality rate (NMR) has also steadily declined, (from 39 to 21 per 1,000 LB). [13-15]. Being an important determinant of neonatal mortality, preterm birth has become a greater contributor to under-5 mortality over time.[16] If we do not consider interventions to address preterm births, it would be difficult to achieve Nepal's Sustainable Development Goal (SDG) that aims to reduce the neonatal mortality to 12 per 1000 LB and under-5 mortality to 28 per 1000 LB by 2030.[17]

There are very few studies on the prevalence or risk factors for preterm birth in Nepal,[18, 19] and those that exist have limitations. First, those studies are hospital based. Women enrolled in hospitals during delivery may suffer from systematic recall bias, where women having a preterm birth might report differently from women with term births. Also, at the time of delivery, women might have recall issues in reporting their date of last menstrual period (LMP). Most important, enrolling at facilities has a selection bias, where the preterm births delivered

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3 at home or on-the-way to facilities are missed, possibly leading to underestimation of the  
4 prevalence and a different distribution of risk factors. Second, previous studies have included  
5 deliveries taken from urban tertiary hospitals in Nepal. Around 80% of the Nepalese population  
6 resides in rural areas[20] and do not have access to delivery services at tertiary centers.  
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8 Moreover, in rural areas, only 47% of deliveries are assisted by skilled birth attendants. [14]  
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10 So, the findings from those studies may not be representative of rural Nepal. Third, since the  
11 women's enrollment was during delivery, they looked at only risk factors that did not vary in  
12 pregnancy and did not analyze changing symptoms, behaviors, and maternal weight gain  
13 throughout pregnancy. Some of these symptoms may be indicative of conditions that can be  
14 addressed by antenatal care. The objective of our study was to estimate the prevalence and  
15 identify predictors/risk factors of spontaneous preterm births in rural Nepal. Understanding and  
16 addressing such risk factors is critical to addressing neonatal and child mortality and morbidity,  
17 particularly in resource-poor settings like Nepal.  
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## 26 **METHODS:**

### 27 **Study Design**

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32 This is a secondary data analysis with data taken from the Nepal Oil Massage Study (NOMS),  
33 which is a cluster-randomized community-based trial (ClinicalTrials.gov, NCT01177111) on  
34 the impact of sunflower seed oil versus standard of care mustard seed oil for neonatal massage  
35 on neonatal mortality and morbidity in rural Sarlahi district of Nepal. This study began by  
36 identifying married women of childbearing age (15 to 40 years) who consented to pregnancy  
37 surveillance. This involved following them every 5 weeks to see whether they became  
38 pregnant, based on a positive pregnancy test offered by the study team if a woman reported  
39 missing a period. If pregnant, they were consented and enrolled in the trial. During enrollment,  
40 demographic data, socioeconomic status, reproductive history, and date of last menstruation  
41 were collected. 123 women (0.3%) refused to be followed after enrollment. Those who  
42 consented were visited monthly by a field worker until the pregnancy outcome occurred or the  
43 study ended. During these monthly visits, field workers asked some basic questions about signs  
44 and symptoms of morbidity during the previous 30-day period. At these visits, women also had  
45 their weight and blood pressure (BP)/pulse measured, and body temperature recorded. Women  
46 reporting signs of morbidity and indicating that these signs were currently present were referred  
47 to the local health post or Primary Health Center. Women with fever or elevated blood pressure  
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3 as measured by study staff were similarly referred for care but continued to be included in the  
4 study.  
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8 As soon as possible after labor began or the baby was delivered, family members or neighbors  
9 notified the local female study worker of the birth. She notified a specially trained team who  
10 visited the mother and infant as soon after birth as possible. They measured infant weight and  
11 time of weight measurement after birth, determined sex of the newborn and whether the baby  
12 was a singleton or multiple birth.  
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### 17 **Setting and Participants**

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20 The study cohort consists of 40,119 pregnancies among married women of child-bearing age,  
21 living in 34 Village Development Committees (VDCs) of Sarlahi district, enrolled from  
22 September 9, 2010, to Jan 16, 2017, in the NOMS study. Pregnancies were followed monthly  
23 until delivery. Live births were categorized as term or preterm. Pregnancies ending in  
24 miscarriage, abortion and stillbirths (SB) were excluded from the analysis. Stillbirths were not  
25 included because the etiology of these may be quite different from those of preterm births.  
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### 32 **Variables**

#### 33 Outcome Variable

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35 The main outcome variable is spontaneous preterm birth among pregnancies that produced at  
36 least one live born infant, defined as pregnancies ending less than 259 gestational days from  
37 the first day of LMP date. Live births were based on women's self-report. They were asked if  
38 the baby moved, cried or breathed after birth. If they said "yes" to one or more of these, the  
39 birth was recorded as a live birth. For gestational age (GA), women were asked about their  
40 LMP during enrollment, and the GA at outcome was calculated as the difference between  
41 reported LMP and the date of the child's birth. Preterm births were classified as spontaneous  
42 or non-spontaneous (caesarian section or/and induction), and only spontaneous preterm births  
43 were included in the regression analysis.  
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#### 54 Independent Variables

55 Through literature review and expert opinion, certain factors were included in the analysis of  
56 predictors. [21] These can be categorized into pregnancy non-varying and pregnancy-varying  
57 variables. Pregnancy non-varying variables included sociodemographic, prior pregnancy  
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3 history, current pregnancy and child related variables that do not change during pregnancy.  
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5 Pregnancy-varying variables included signs and symptoms of morbidity in pregnancy, and  
6  
7 maternal weight.  
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10 Sociodemographic variables like maternal age at LMP, caste/religion, maternal education,  
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12 wealth quintile and maternal height were explored. Maternal age was categorized as less than  
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14 18, 18-35 and more than 35 years to assess the association of very young women and older  
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16 women with preterm births. Caste/religion of the mothers (Brahmin /Chhetri, Vaishya, Shudra,  
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18 Muslim and others) were used as per the caste category system in Nepal. [22] Maternal  
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20 education (No schooling, 1-5 years and more than 5 years); and maternal height (<145 cm,  
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22 145-<150 and  $\geq 150$ ) were used. Household wealth status was measured in quintiles based on  
23  
24 a standardized score using principal components analysis of household assets. [23]  
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26 Prior pregnancy related variables like parity (1-4, more than 4, prior pregnant but not resulting  
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28 in live or still birth and no prior pregnant); interpregnancy interval (IPI) defined as the time  
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30 since the end of last pregnancy to the date of LMP of the current pregnancy, regardless of the  
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32 outcome (<18, 18-36, and >36 months); any prior live born child who died (No prior LB died  
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34 and Died); any prior pregnancy that ended in a SB (No prior SB and SB); any prior pregnancy  
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36 ending in miscarriage (No prior miscarriage and Miscarriage) ; and any prior pregnancy that  
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38 ended in multiples (No prior multiples and Multiples) were assessed.  
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40 Current pregnancy related variables like tobacco intake (ever used any tobacco products during  
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42 this pregnancy- Yes and No), and alcohol intake (ever used alcohol during this pregnancy- Yes  
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44 and No) were assessed. Child-level variables like multiple birth (singleton and twin/triplet),  
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46 and sex of the child (male and female) were included. We used the category with the low risk  
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48 according to literature of similar settings, to be the reference group if there was no clear  
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50 hierarchy of risk (such as maternal age, caste) but selected the most at risk group for those  
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52 where a hierarchy existed (such as maternal education, wealth quintile, maternal height).  
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54 Current pregnancy related variables like tobacco and alcohol intake were not included in the  
55  
56 regressions because rates of use were very low. Only 0.3% consumed alcohol and only 1.1%  
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58 used tobacco. Other current pregnancy related variables like number of antenatal care (ANC)  
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60 visits and place of delivery were shown in descriptive, but omitted from inferential analysis

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3 because in this setting, women with spontaneous preterm births could have missed the 4th ANC  
4 visit in the 9<sup>th</sup> month and preterm birth could be the cause of a lower number of visits. For place  
5 of delivery, spontaneous preterm births were more likely to be delivered at home or on the way  
6 to the facility, because many births in this environment are not planned to occur in a facility.  
7 However, we also included these variables in the multivariable regressions and provided these  
8 as supplemental analyses because ANC may be important in reducing preterm birth.  
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15 Symptoms of morbidity during pregnancy such as sexually transmitted diseases (STI),  
16 respiratory illness, gastrointestinal (GI) illness, poor appetite, nausea and vomiting, vaginal  
17 bleeding, swelling of hands or face, high systolic and diastolic blood pressure were assessed.  
18 All these variables were assessed in the 2<sup>nd</sup> and 3<sup>rd</sup> trimester, and so labelled as – Problem in  
19 at least one visit of the 2<sup>nd</sup> trimester- Yes or No, and Problem in at least one visit in the 3<sup>rd</sup>  
20 trimester- Yes or No. We did not include symptoms of morbidities in the 1<sup>st</sup> trimester because  
21 only 41% women were enrolled in the 1<sup>st</sup> trimester, and so 59% missed symptom information  
22 in the 1<sup>st</sup> trimester. Maternal weight gain was defined as the average weight in the 3<sup>rd</sup> trimester  
23 minus the average weight in the 2<sup>nd</sup> trimester. For measurement of these symptom variables,  
24 field workers asked if women had symptoms of morbidity at any time in the past 30 days, at  
25 each monthly visit during pregnancy. STI was defined as painful or burning urination, or foul  
26 smelling vaginal discharge. Respiratory illness was defined as persistent cough, or difficult or  
27 rapid breathing, or wheezing/grunting, or shortness of breath. GI illness was defined as watery  
28 stools (4 or more times in a day or blood or white mucus in the stool). Appetite related illness  
29 was defined as poor appetite, nausea or vomiting. Vaginal bleeding was defined as spots of  
30 blood from the vagina. Swelling was defined as swelling of hands and/or face. Foot/leg  
31 swelling was excluded since it is common during pregnancy and not indicative of underlying  
32 disease. BP measurements were categorized as high systolic BP if the systolic measurement  
33 was  $\geq 140$  mmHg, and high diastolic BP if diastolic measurement was  $\geq 90$  mmHg at any  
34 monthly visit within the 2<sup>nd</sup> or 3<sup>rd</sup> trimester.  
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## 51 **Statistical Methods**

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54 First, a descriptive analysis was done to show the frequencies of pregnancy non-varying  
55 variables (socio demographic, prior pregnancy related, current pregnancy and child related)  
56 and pregnancy varying variables (symptoms and maternal weight) by spontaneous preterm and  
57 term births. Second, bivariable GEE Poisson regression with robust variance was used to  
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3 examine associations between each risk factor and the outcome to get an unadjusted risk ratio.  
4 Since the prevalence of our outcome was more than 10%, we used Poisson regression with  
5 robust variance because we wanted to report associations as risk ratios. Third, multivariable  
6 GEE Poisson regression with robust variance was used including variables that were significant  
7 in the bivariable models, to get the adjusted risk ratios (ARR). GEE was used because in the  
8 study, 52% women had multiple pregnancies. Since our unit of analysis is pregnancy and  
9 pregnancies were nested within women, women's id variable was used as cluster for GEE  
10 modelling.  
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19 We included a larger number of potential risk factors to provide a general description of the  
20 study population but did not include all of these in the regression analysis. Some variables were  
21 highly correlated with each other (such as some reproductive history variables) and we chose  
22 just to include one rather than all, and for others, the prevalence was so low that we did not  
23 think helpful to include in the regression (for example, smoking and alcohol use). Some of the  
24 variables in the unadjusted analysis were not included in the regression because they were not  
25 statistically significant in the unadjusted analysis. For example, prior pregnancy ending in  
26 miscarriage, stillbirth or a prior multiple birth were not included (as these were highly  
27 correlated with each other and not statistically significant in crude models). We did include  
28 death of a prior livebirth, which was significant in the crude model.  
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38 The descriptive analysis had 31,851 pregnancies. In the regression analysis, we excluded the  
39 1093 pregnancies (3.4%) that ended in caesarian section, induction or both, which leaves  
40 30,758 for analysis. Then, 30.7% out of 30,758 ( 20.2% missing morbidity in 2<sup>nd</sup> trimester due  
41 to enrollment only in 3<sup>rd</sup> trimester, 9.4% missing morbidity in 3<sup>rd</sup> trimester and 1.1% missing  
42 other variables) were missing in the regression analysis, and so the final multivariable  
43 regression analysis excluded those 9,461 pregnancies, and consisted of 21,297 pregnancies.  
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### 49 **Patient and Public Involvement**

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52 Patients or the public were not involved in the design, or conduct, or reporting, or  
53 dissemination plans of this study.  
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## 56 **RESULTS:**

### 57 **Participants**

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3 The analytic population is 31,851 pregnancies that ended in at least one live birth and had  
4 information on gestational age at outcome. The detailed flow chart is given in Figure 1. Most  
5 women were enrolled in the 1<sup>st</sup> and 2<sup>nd</sup> trimester (41% each), followed by the 3<sup>rd</sup> trimester  
6 (18%). Overall, the mean gestational age at enrollment was 18 weeks. For 1<sup>st</sup>, 2<sup>nd</sup> and 3<sup>rd</sup>  
7 trimesters, the mean GA at enrollment were 9, 19 and 34 weeks respectively. 52% women  
8 (33% with two pregnancies, 14% with three pregnancies, 4% with four pregnancies and 1%  
9 with more than four pregnancies) contributed more than one pregnancy to the study.

## 16 **Descriptive Analysis**

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19 For pregnancy non-varying variables, as seen in Table 1, 15% of women were younger (less  
20 than 18) and 2% women were older (more than 35 years of age). 9% of women were Muslim  
21 caste/religion. Two thirds of women did not go to school, whereas only nearly one fourth had  
22 an education of more than five years. 15% of women had height <145cm. About a third (29%)  
23 of women had their first pregnancy in this study and 64% had one to four prior live or still  
24 births. Among those who had a previous pregnancy, 6% had prior still birth, 16% experienced  
25 miscarriage and 16% had a live birth that died, and only 1% had prior multiples. Half the  
26 women had an interpregnancy interval of less than 18 months, and 28% of women had four or  
27 more ANC visits. Half of the babies were born at home and 2% were born on the way to a  
28 facility or outdoors. Only 1.1% consumed tobacco and only 0.3% consumed alcohol during  
29 pregnancy. Half of the current pregnancies (51%) resulted in male children, and less than 1%  
30 resulted in multiple births. Only 3.4% of pregnancies underwent either caesarian section or  
31 induction or both.

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34 For pregnancy-varying variables, as seen in Table 2, poor appetite, nausea and vomiting was  
35 the most commonly reported symptom in both the second (39%) and third trimesters (20%);  
36 and vaginal bleeding was the least reported symptom (1.2% in the second and 0.6% in the third  
37 trimester). Very few women had high systolic blood pressure (0.5% and 0.8%) and high  
38 diastolic blood pressure (1.5% and 2.9%) in second and third trimesters respectively. The  
39 average weight gained by women from second to third trimester was 3.5 kg.

**Table 1: Distribution of Pregnancy non-varying Variables by preterm and term births**

| Variables                                      | Categories                                       | Total           | Term          | Preterm      |
|--|--|-----------------|---------------|--------------|
|  |  | N=31,851        | N=27,059      | N=4,792      |
|  |  | N (%)           | N (%)         | N (%)        |
| Maternal Age at LMP                            | 18 to 35   | 26,206 (82.3)   | 22,423 (82.9) | 3,783 (78.9) |
|  | Less than 18                                     | 4,946 (15.5)    | 4,100 (15.2)  | 846 (17.7)   |
|  | More than 35                                     | 699 (2.2)       | 536 (2.0)     | 163 (3.4)    |
| Caste/Religion                                 | Brahmin and Chhetri                              | 963 (3.0)       | 857 (3.2)     | 106 (2.2)    |
|  | Vaishya  | 22,946 (72.0)   | 19,701 (72.8) | 3,245 (67.7) |
|  | Shudra   | 4,922 (15.5)    | 4,111 (15.2)  | 811 (16.9)   |
|  | Muslim and others                                | 2,989 (9.4)     | 2,365 (8.7)   | 624 (13.0)   |
|  | Missing  | 31 (0.1)        | 25 (0.1)      | 6 (0.1)      |
| Maternal Education                             | No schooling                                     | 21,427 (67.3)   | 17,915 (66.2) | 3,512 (73.3) |
|  | 1 to 5 years                                     | 2,713 (8.5)     | 2,330 (8.6)   | 383 (8.0)    |
|  | More than 5 years                                | 7,681 (24.1)    | 6,786 (25.1)  | 895 (18.7)   |
|  | Missing  | 30 (0.1)        | 28 (0.1)      | 2 (0.0)      |
| Quintiles of Wealth                            | Poorest  | 6,510 (20.4)    | 5,340 (19.7)  | 1,170 (24.4) |
|  | Poor   | 6,380 (20.0)    | 5,403 (20.0)  | 977 (20.4)   |
|  | Middle   | 6,320 (19.8)    | 5,314 (19.6)  | 1,006 (21.0) |
|  | Richer   | 6,296 (19.8)    | 5,470 (20.2)  | 826 (17.2)   |
|  | Richest  | 6,324 (19.9)    | 5,516 (20.4)  | 808 (16.9)   |
|  | Missing  | 21 (0.1)        | 16 (0.1)      | 5 (0.1)      |
| Maternal Height (cms)                          | <145   | 4,689 (14.7)    | 3,885 (14.4)  | 800 (16.7)   |
|  | 145-<150   | 9,559 (29.9)    | 8,025 (29.7)  | 1,527 (31.9) |
|  | >=150  | 17,581 (55.1)   | 15,111 (55.8) | 2,454 (51.2) |
|  | Missing  | 51 (0.2)        | 38 (0.14)     | 11 (0.2)     |
| Parity including both LB and SB, at Enrollment | Parity 1 to 4                                    | 20,317 (63.8)   | 17,366 (64.2) | 2,951 (61.6) |
|  | More than 4                                      | 1,383 (4.3)     | 1,117 (4.1)   | 266 (5.6)    |
|  | Prior Pregnant but parity 0                      | 787 (2.5)       | 672 (2.5)     | 115 (2.4)    |
|  | No Prior Pregnant                                | 9,195 (28.9)    | 7,769 (28.7)  | 1,426 (29.8) |
|  | Missing  | 169 (0.5)       | 135 (0.5)     | 34 (0.7)     |
|  | Interpregnancy Interval based on maternal recall | 18 to 36 months | 7,927 (24.9)  | 6,787 (25.1) |
| Any deaths among Prior LB                      | Less than 18 months                              | 11,461 (36.0)   | 9,701 (35.9)  | 1,760 (36.7) |
|  | More than 36 months                              | 3,256 (10.2)    | 2,794 (10.3)  | 462 (9.6)    |
|  | No Prior Pregnancy                               | 9,195 (28.9)    | 7,769 (28.7)  | 1,426 (29.8) |
|  | Missing  | 12 (0.0)        | 8 (0.0)       | 4 (0.1)      |
|  | Prior LB but not died                            | 17,488 (54.9)   | 14,999 (55.4) | 2,489 (51.9) |
| Any prior pregnancy ended in SB                | Prior LB died                                    | 3,618 (11.4)    | 2,999 (11.1)  | 619 (12.9)   |
|  | Prior Pregnancy but no LB                        | 1,073 (3.4)     | 909 (3.4)     | 164 (3.4)    |
|  | No prior pregnancy                               | 9,195 (28.9)    | 7,769 (28.7)  | 1,426 (29.8) |
|  | Missing  | 477 (1.5)       | 383 (1.4)     | 94 (2.0)     |
|  | Prior Pregnancy but no SB                        | 21,270 (66.8)   | 18,127 (67.0) | 3,143 (65.6) |
|  | Prior SB   | 1,371 (4.3)     | 1,150 (4.2)   | 221 (4.6)    |
| Any prior pregnancy ended in SB                | No prior pregnancy                               | 9,195 (28.9)    | 7,769 (28.7)  | 1,426 (29.8) |
|  | Missing  | 15 (0.0)        | 13 (0.0)      | 2 (0.0)      |

| Variables                                   | Categories                         | Total         | Term          | Preterm      |
|---|------------------------------------|---------------|---------------|--------------|
|   |                                    | N=31,851      | N=27,059      | N=4,792      |
|   |                                    | N (%)         | N (%)         | N (%)        |
| Any prior pregnancy ended in miscarriage    | Prior Pregnancy but no miscarriage | 19,025 (59.7) | 16,176 (59.8) | 2,849 (59.5) |
|   | Prior miscarriage                  | 3,621 (11.4)  | 3,104 (11.5)  | 517 (10.8)   |
|   | No prior pregnancy                 | 9,195 (28.9)  | 7,769 (28.7)  | 1,426 (29.8) |
|   | Missing                            | 10 (0.0)      | 10 (0.0)      | 0 (0.0)      |
| Any prior pregnancy ended in multiples      | Prior Pregnancy but no multiples   | 22,343 (70.1) | 19,030 (70.3) | 3,313 (69.1) |
|   | Prior multiples                    | 292 (0.9)     | 241 (0.9)     | 51 (1.1)     |
|   | No prior pregnancy                 | 9,195 (28.9)  | 7,769 (28.7)  | 1,426 (29.8) |
|   | Missing                            | 21 (0.1)      | 19 (0.1)      | 2 (0.0)      |
| Number of ANC visits                        | No visit                           | 5,520 (17.3)  | 4,524 (16.7)  | 996 (20.8)   |
|   | 1 visit                            | 4,146 (13.0)  | 3,420 (12.6)  | 726 (15.2)   |
|   | 2-3 visit                          | 9,779 (30.7)  | 8,158 (30.1)  | 1,621 (33.8) |
|   | 4 or more                          | 8,909 (28.0)  | 8,021 (29.6)  | 888 (18.5)   |
|   | Missing                            | 3,497 (11.0)  | 2,936 (10.9)  | 561 (11.7)   |
| Place of Delivery                           | Home/Maiti                         | 15,776 (49.5) | 13,270 (49.0) | 2,506 (52.3) |
|   | HP/Clinic/Hospital                 | 12,016 (37.7) | 10,406 (38.5) | 1,610 (33.6) |
|   | Way to Facility/Outdoors           | 610 (1.9)     | 486 (1.8)     | 124 (2.6)    |
|   | Missing                            | 3,449 (10.8)  | 2,897 (10.7)  | 552 (11.5)   |
| Bidi or tobacco use in pregnancy            | No                                 | 31,498 (98.9) | 26,789 (99.0) | 4,709 (98.3) |
|   | Yes                                | 353 (1.1)     | 270 (1.0)     | 83 (1.7)     |
| Alcohol use (jaard or rakshi) in pregnancy? | No                                 | 31,756 (99.7) | 26,982 (99.7) | 4,774 (99.6) |
|   | Yes                                | 95 (0.3)      | 77 (0.3)      | 18 (0.4)     |
| Multiple Birth                              | Singleton                          | 31,587 (99.2) | 26,946 (99.6) | 4,641 (96.8) |
|   | Twin/Triplet                       | 264 (0.8)     | 113 (0.4)     | 151 (3.2)    |
| Sex of the child                            | Female                             | 15,182 (47.7) | 13,063 (48.3) | 2,119 (44.2) |
|   | Male                               | 16,306 (51.2) | 13,794 (51.0) | 2,512 (52.4) |
|   | Twin/Triplet                       | 264 (0.8)     | 113 (0.4)     | 151 (3.2)    |
|   | Missing                            | 99 (0.3)      | 89 (0.3)      | 10 (0.2)     |
| Induction or CS done                        | Only Induction                     | 193 (0.6)     | 166 (0.6)     | 27 (0.6)     |
|   | Only CS                            | 868 (2.7)     | 735 (2.8)     | 133 (2.8)    |
|   | Both Induction and CS              | 32 (0.1)      | 28 (0.1)      | 4 (0.08)     |
|   | None                               | 30,758 (96.6) | 26130 (96.6)  | 4628 (96.6)  |

**Table 2: Distribution of pregnancy-varying variables by preterm and term births**

| Variables  |         | Total<br>N=31,851<br>N (%) | Term<br>N=27,059<br>N (%) | Preterm<br>N=4,792<br>N (%) |
|--|---------|----------------------------|---------------------------|-----------------------------|
| STI in at least one visit of 2nd trimester?                              | No      | 20,823 (65.4)              | 17,497 (64.7)             | 3,326 (69.4)                |
|  | Yes     | 4,593 (14.4)               | 3,855 (14.2)              | 738 (15.4)                  |
|  | Missing | 6,435 (20.2)               | 5,707 (21.1)              | 728 (15.2)                  |
| STI in at least one visit of 3rd trimester?                              | No      | 25,931 (81.4)              | 22,512 (83.2)             | 3,419 (71.3)                |
|  | Yes     | 2,963 (9.3)                | 2,569 (9.5)               | 394 (8.2)                   |
|  | Missing | 2,957 (9.3)                | 1,978 (7.3)               | 979 (20.4)                  |
| Respiratory Problems in at least one visit of 2nd trimester?             | No      | 17,963 (56.4)              | 15,081 (55.7)             | 2,882 (60.1)                |
|  | Yes     | 7,452 (23.4)               | 6,271 (23.2)              | 1,181 (24.6)                |
|  | Missing | 6,436 (20.2)               | 5,707 (21.1)              | 729 (15.2)                  |
| Respiratory Problems in at least one visit of 3rd trimester?             | No      | 22,860 (71.8)              | 19,743 (73.0)             | 3,117 (65.0)                |
|  | Yes     | 6,034 (18.9)               | 5,338 (19.7)              | 696 (14.5)                  |
|  | Missing | 2,957 (9.3)                | 1,978 (7.3)               | 979 (20.4)                  |
| GI Problems in at least one visit of 2nd trimester?                      | No      | 22,742 (71.4)              | 19,136 (70.7)             | 3,606 (75.3)                |
|  | Yes     | 2,673 (8.4)                | 2,216 (8.2)               | 457 (9.5)                   |
|  | Missing | 6,436 (20.2)               | 5,707 (21.1)              | 729 (15.2)                  |
| GI Problems in at least one visit of 3rd trimester?                      | No      | 26,152 (82.1)              | 22,712 (83.9)             | 3,440 (71.8)                |
|  | Yes     | 2,742 (8.6)                | 2,369 (8.8)               | 373 (7.8)                   |
|  | Missing | 2,957 (9.3)                | 1,978 (7.3)               | 979 (20.4)                  |
| Poor appetite, nausea & vomiting in at least one visit of 2nd trimester? | No      | 13,121 (41.2)              | 10,814 (40.0)             | 2,307 (48.1)                |
|  | Yes     | 12,295 (38.6)              | 10,538 (38.9)             | 1,757 (36.7)                |
|  | Missing | 6,435 (20.2)               | 5,707 (21.1)              | 728 (15.2)                  |
| Poor appetite, nausea & vomiting in at least one visit of 3rd trimester? | No      | 22,486 (70.6)              | 19,437 (71.8)             | 3,049 (63.6)                |
|  | Yes     | 6,409 (20.1)               | 5,645 (20.9)              | 764 (15.9)                  |
|  | Missing | 2,956 (9.3)                | 1,977 (7.3)               | 979 (20.4)                  |
| Vaginal Bleeding in at least one visit of 2nd trimester?                 | No      | 25,042 (78.6)              | 21,036 (77.7)             | 4,006 (83.6)                |
|  | Yes     | 373 (1.2)                  | 315 (1.2)                 | 58 (1.2)                    |
|  | Missing | 6,436 (20.2)               | 5,708 (21.1)              | 728 (15.2)                  |
| Vaginal Bleeding in at least one visit of 3rd trimester?                 | No      | 28,716 (90.2)              | 24,938 (92.2)             | 3,778 (78.8)                |
|  | Yes     | 178 (0.6)                  | 143 (0.5)                 | 35 (0.7)                    |
|  | Missing | 2,957 (9.3)                | 1,978 (7.3)               | 979 (20.4)                  |
| Swelling in at least one visit of 2nd trimester?                         | No      | 24,846 (78.0)              | 20,904 (77.3)             | 3,942 (82.3)                |
|  | Yes     | 571 (1.8)                  | 448 (1.7)                 | 123 (2.6)                   |
|  | Missing | 6,434 (20.2)               | 5,707 (21.1)              | 727 (15.2)                  |

| Variables   |                     | Total<br>N=31,851<br>N (%) | Term<br>N=27,059<br>N (%) | Preterm<br>N=4,792<br>N (%) |
|---|---------------------|----------------------------|---------------------------|-----------------------------|
| Swelling in at least one visit of 3rd trimester?  | No                  | 27,754 (87.1)              | 24,126 (89.2)             | 3,628 (75.7)                |
|   | Yes                 | 1,141 (3.6)                | 956 (3.5)                 | 185 (3.9)                   |
|   | Missing             | 2,956 (9.3)                | 1,977 (7.3)               | 979 (20.4)                  |
| High Systolic BP in 2nd trimester?  | Normal Systolic BP  | 25,260 (79.3)              | 21,217 (78.4)             | 4,043 (84.4)                |
|   | High Systolic BP    | 158 (0.5)                  | 136 (0.5)                 | 22 (0.5)                    |
|   | Missing             | 6,433 (20.2)               | 5,706 (21.1)              | 727 (15.2)                  |
|   | Normal Systolic BP  | 28,659 (90.0)              | 24,905 (92.0)             | 3,754 (78.3)                |
| High Systolic BP in 3rd trimester?  | High Systolic BP    | 241 (0.8)                  | 181 (0.7)                 | 60 (1.3)                    |
|   | Missing             | 2,951 (9.3)                | 1,973 (7.3)               | 978 (20.4)                  |
|   | Normal diastolic BP | 24,945 (78.3)              | 20,976 (77.5)             | 3,969 (82.8)                |
|   | High diastolic BP   | 473 (1.5)                  | 377 (1.4)                 | 96 (2.0)                    |
| High diastolic BP in 2nd trimester?   | Missing             | 6,433 (20.2)               | 5,706 (21.1)              | 727 (15.2)                  |
|   | Normal diastolic BP | 27,982 (87.9)              | 24,360 (90.0)             | 3,622 (75.6)                |
|   | High diastolic BP   | 918 (2.9)                  | 726 (2.7)                 | 192 (4.0)                   |
|   | Missing             | 2,951 (9.3)                | 1,973 (7.3)               | 978 (20.4)                  |
| Average weight in 3rd trimester minus Average weight in 2nd trimester in kg (Mean (SD)) |                     | 3.5 (2.1)                  | 3.6 (2.1)                 | 2.9 (2.2)                   |



## Outcome data

There were 4,792 preterm births out of 31,851 pregnancies with at least one LB. Hence, the prevalence of preterm birth was 15% (95% CI: 14.6%, 15.4%) among the pregnancies enrolled between September 9, 2010, to January 16, 2017. Spontaneous preterm birth was 14.5% and non-spontaneous preterm birth was 0.5%. On looking at severity of spontaneous preterm birth, the prevalence were 0.5%, 1.4% and 2.1% and 10.5% for extreme PTB (<28 weeks), very PTB (28-<32 weeks), moderate PTB (32-<34 weeks) and late PTB (34-<37 weeks) respectively.

## Main results

The main results are shown in Table 3. Pregnancy non-varying variables that increased the risk of spontaneous preterm were maternal age less than 18 (ARR=1.13, 95% CI: 1.02-1.26); being Muslim compared to Brahmin and Chhetri (1.53, 1.16-2.01); first pregnancy as compared to parity 1 to 4 (1.15, 1.04-1.28); having a multiple birth (4.91, 4.20-5.75) and having a male child (1.10, 1.02-1.17). Pregnancy non-varying variables that decreased the risk of spontaneous preterm were maternal education of more than 5 years (0.81, 0.73-0.90); maternal height of  $\geq 150$  cm (0.89, 0.81-0.98) and being wealthier: richer (0.83, 0.74-0.93) wealth quintile compared to the poorest wealth quintile. Pregnancy non-varying variables that showed no association with spontaneous preterm births in the bivariable/unadjusted models are any prior pregnancy ending in SB, any prior pregnancy ending in multiples, and any prior pregnancy ending in miscarriage, and interpregnancy interval. The pregnancy non-varying variable that showed an association in the bivariable model, but not in the multivariable models was any prior pregnancy ending in death for a live birth.

For morbidity symptoms, some increased the risk of preterm, and all of these showed increased risk when symptoms were present in the 3<sup>rd</sup> trimester. Having vaginal bleeding (ARR= 1.53, 95% CI: 1.08-2.18); swelling (1.37, 1.17-1.60); high systolic BP (1.47, 1.08-2.01) and high diastolic BP (1.41, 1.17-1.70) in the 3<sup>rd</sup> trimester significantly increased the risk of spontaneous preterm. Some symptom variables significantly decreased the risk of spontaneous preterm. Having respiratory problem in the 3<sup>rd</sup> trimester (0.86, 0.79-0.94); and having poor appetite, nausea and vomiting in the 2<sup>nd</sup> trimester (0.86, 0.80-0.92) and in the 3<sup>rd</sup> trimester (0.86, 0.79-0.94) decreased the risk of spontaneous preterm. Symptom variables that showed no association with spontaneous preterm were STI and GI problems. Symptom variables that were

significant in the bivariable model, but not significant in the multivariable models were swelling in the 2<sup>nd</sup> trimester and diastolic blood pressure in the 2<sup>nd</sup> trimester. For maternal weight, higher weight gain from the 2<sup>nd</sup> to the 3<sup>rd</sup> trimester was associated with a decreased the risk of spontaneous preterm (0.89, 0.87-0.90).

To examine the possible bias associated with exclusion of pregnancies with missing data, we compared characteristics of women excluded in the regression analysis (n=9,461) (mainly because of missing morbidity in 2<sup>nd</sup> trimester due to late enrollment) with those included in the regression analysis (n=21,297) (supplementary Table S1). The women excluded in the regression analysis were slightly better off than those included in the regression based on education and socioeconomic status but most relevant, the spontaneous preterm prevalence was 17.9% for those excluded in the regression compared to 13.8% included in the regression.

We also reran the regression model including number of ANC visits. The fewer the number of ANC visits, the higher the risk of spontaneous preterm birth (Table S2). The other regression coefficients did not change in any qualitative way. This could be due to fewer ANC visits putting women at higher risk for spontaneous preterm birth as services provided in ANC (counseling, iron folic acid tablets, blood pressure and weight measurements) are provided less often, but this association may also be due to a shorter duration of pregnancy leading to less time available for ANC visits.

**Table 3: Crude and Adjusted Risk Ratios for associations between risk factors and spontaneous preterm birth**

| Name of Variables           | Categories          | Unadjusted Model<br>Risk Ratio (95% CI) | Adjusted Model<br>(N=21,297)<br>Risk Ratio (95% CI) |
|-----------------------------|---------------------|---|---|
| Maternal Age at LMP         | 18 to 35            | 1                                       | 1   |
|                             | Less than 18        | 1.19*** [1.11,1.28]                     | 1.13* [1.02,1.26]                                   |
|                             | More than 35        | 1.57*** [1.36,1.81]                     | 1.22 [0.98,1.51]                                    |
| Caste/Religion Categories   | Brahmin and Chhetri | 1                                       | 1   |
|                             | Vaishya             | 1.33** [1.09,1.62]                      | 1.23 [0.95,1.59]                                    |
|                             | Shudra              | 1.55*** [1.26,1.90]                     | 1.23 [0.94,1.62]                                    |
|                             | Muslim and others   | 1.96*** [1.60,2.42]                     | 1.53** [1.16,2.01]                                  |
| Mother's Years of Education | No schooling        | 1                                       | 1   |
|                             | 1 to 5 years        | 0.86** [0.78,0.95]                      | 0.91 [0.80,1.03]                                    |
|                             | More than 5 years   | 0.71*** [0.66,0.76]                     | 0.81*** [0.73,0.90]                                 |
| Quintiles of Wealth         | Poorest             | 1                                       | 1   |
|                             | Poor                | 0.86*** [0.79,0.93]                     | 0.90* [0.82,1.00]                                   |
|                             | Middle              | 0.89** [0.82,0.96]                      | 0.95 [0.86,1.05]                                    |

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| Name of Variables  | Categories                                  | Unadjusted Model<br>Risk Ratio (95% CI) | Adjusted Model<br>(N=21,297)<br>Risk Ratio (95% CI) |
|--|---|---|---|
| Mother's height(centimeter)  | Richer                                      | 0.73*** [0.67,0.79]                     | 0.83** [0.74,0.93]                                  |
|  | Richest                                     | 0.71*** [0.65,0.77]                     | 0.88* [0.78,1.00]                                   |
|  | <145  | 1                                       | 1   |
|  | 145-<150                                    | 0.93 [0.86,1.01]                        | 0.98 [0.88,1.08]                                    |
| Parity including both LB and SB, at Enrollment                           | >=150                                       | 0.81*** [0.75,0.87]                     | 0.89* [0.81,0.98]                                   |
|  | Parity 1 to 4                               | 1                                       | 1   |
|  | More than 4                                 | 1.32*** [1.17,1.48]                     | 1.17 [0.99,1.37]                                    |
|  | Prior Pregnant but parity 0                 | 1.02 [0.85,1.22]                        | 0.92 [0.62,1.37]                                    |
| Interpregnancy Intervals   | No Prior Pregnant                           | 1.10** [1.04,1.17]                      | 1.15** [1.04,1.28]                                  |
|  | 18 to 36 months                             | 1                                       | 1   |
|  | Less than 18 months                         | 1.07 [0.99,1.14]                        | 1.08 [0.99,1.18]                                    |
|  | More than 36 months                         | 0.98 [0.89,1.09]                        | 0.9 [0.79,1.02]                                     |
| Any death among prior LB   | No Prior Pregnancy                          | 1.11** [1.03,1.20]                      | 1 [1.00,1.00]                                       |
|  | Prior LB but not died                       | 1                                       | 1   |
|  | Prior LB died                               | 1.19*** [1.09,1.29]                     | 1.07 [0.97,1.19]                                    |
|  | Prior Pregnancy but no LB                   | 1.07 [0.92,1.25]                        | 1.06 [0.75,1.49]                                    |
| Any prior pregnancy ended in SB  | No prior pregnancy                          | 1.12*** [1.06,1.19]                     | 1 [1.00,1.00]                                       |
|  | Prior Pregnancy but no SB                   | 1                                       |   |
|  | Prior SB                                    | 1.08 [0.94,1.23]                        |   |
|  | No Prior Pregnancy                          | 1.08** [1.02,1.15]                      |   |
| Any prior pregnancy ended in miscarriage                                 | Prior Pregnancy but no miscarriage          | 1                                       |   |
|  | Prior miscarriage                           | 0.94 [0.86,1.03]                        |   |
|  | No Prior Pregnancy                          | 1.07* [1.01,1.13]                       |   |
|  | Prior Pregnancy but no multiples            | 1                                       |   |
| Any prior pregnancy ended in multiples                                   | Prior multiples                             | 1.14 [0.87,1.49]                        |   |
|  | No prior pregnancy                          | 1.08** [1.02,1.14]                      |   |
|  | Singleton                                   | 1                                       | 1   |
|  | Twin/Triplet                                | 3.92*** [3.52,4.38]                     | 4.91*** [4.20,5.75]                                 |
| Sex of the child   | Female                                      | 1                                       | 1   |
|  | Male  | 1.10*** [1.04,1.17]                     | 1.10** [1.02,1.17]                                  |
|  | Twin/Triplet                                | 4.13*** [3.69,4.63]                     | 1   |
|  | STI in at least one visit of 2nd trimester? | No                                      | 1   |
| STI in at least one visit of 2nd trimester?                              | Yes   | 0.99 [0.92,1.07]                        |   |
|  | No  | 1                                       |   |
| STI in at least one visit of 3rd trimester?                              | Yes   | 1.01 [0.92,1.12]                        |   |
|  | No  | 1                                       | 1   |
| Respiratory Problems in at least one visit of 2nd trimester?             | Yes   | 1 [0.94,1.06]                           | 1.08 [1.00,1.16]                                    |
|  | No  | 1                                       | 1   |
| Respiratory Problems in at least one visit of 3rd trimester?             | Yes   | 0.85*** [0.79,0.92]                     | 0.86** [0.79,0.94]                                  |
|  | No  | 1                                       |   |
| GI Problems in at least one visit of 2nd trimester?                      | Yes   | 1.08 [0.98,1.18]                        |   |
|  | No  | 1                                       |   |
| GI Problems in at least one visit of 3rd trimester?                      | Yes   | 1.04 [0.94,1.16]                        |   |
|  | No  | 1                                       | 1   |
| Poor appetite, nausea & vomiting in at least one visit of 2nd trimester? | Yes   | 0.81*** [0.77,0.86]                     | 0.86*** [0.80,0.92]                                 |
|  | No  | 1                                       | 1   |

| Name of Variables   | Categories          | Unadjusted Model<br>Risk Ratio (95% CI) | Adjusted Model<br>(N=21,297)<br>Risk Ratio (95% CI) |
|---|---------------------|---|---|
| one visit of 3rd trimester?   | Yes                 | 0.88** [0.82,0.95]                      | 0.86*** [0.79,0.94]                                 |
| Vaginal Bleeding in at least one visit of 2nd trimester?                      | No                  | 1                                       | 1   |
|   | Yes                 | 0.91 [0.71,1.17]                        | 0.84 [0.71,1.17]                                    |
| Vaginal Bleeding in at least one visit of 3rd trimester?                      | No                  | 1                                       | 1   |
|   | Yes                 | 1.44* [1.05,1.98]                       | 1.53*[1.08,2.18]                                    |
| Swelling in at least one visit of 2nd trimester?                              | No                  | 1                                       | 1   |
|   | Yes                 | 1.32*** [1.12,1.55]                     | 1.19 [0.98,1.46]                                    |
| Swelling in at least one visit of 3rd trimester?                              | No                  | 1                                       | 1   |
|   | Yes                 | 1.25** [1.09,1.44]                      | 1.37*** [1.17,1.60]                                 |
| High Systolic BP in 2nd trimester?  | Normal Systolic BP  | 1                                       | 1   |
|   | High Systolic BP    | 0.89 [0.59,1.34]                        | 0.67 [0.40,1.12]                                    |
| High Systolic BP in 3rd trimester?  | Normal Systolic BP  | 1                                       | 1   |
|   | High Systolic BP    | 1.92*** [1.52,2.41]                     | 1.47* [1.08,2.01]                                   |
| High diastolic BP in 2nd trimester?   | Normal diastolic BP | 1                                       | 1   |
|   | High diastolic BP   | 1.34** [1.12,1.60]                      | 1.09 [0.85,1.40]                                    |
| High diastolic BP in 3rd trimester?   | Normal diastolic BP | 1                                       | 1   |
|   | High diastolic BP   | 1.57*** [1.37,1.80]                     | 1.41*** [1.17,1.70]                                 |
| Average weight in 3rd trimester minus<br>Average weight in 2nd trimester (kg) |                     | 0.88*** [0.87,0.90]                     | 0.89*** [0.87,0.90]                                 |

\*  $p < 0.05$ , \*\*  $p < 0.01$ , \*\*\*  $p < 0.001$

## DISCUSSION

Our study is one of the only large-scale studies on preterm births using data from an existing pregnancy surveillance in rural Sarlahi, Nepal. The prevalence of preterm birth is 15%, higher than previous estimates from Nepal [18, 19] which were primarily from urban areas and large hospital-based studies. Our study's strength is that it was population-based and included all home and facility deliveries but is confined to a rural and relatively small geographic area (one third of a district). Our study population is not necessarily representative of all of Nepal, but it is representative of Province 2 in the Terai region within which Sarlahi district is located. For example, the NMR in our study was 31 per 1000 live births. This is similar to the NMR in the 2016 Nepal Demographic Health Survey (NDHS) for Province 2 (30 per 1000). Similarly, 67% of women in our study had no schooling, slightly higher than the 61% in the NDHS for Province 2. NDHS did not provide data on ANC 4+ for Province 2 but rural areas of Nepal had 62% coverage of ANC 4+. It should be noted in our study that health care seeking in pregnancy is low considering the low rates of 4 or more ANC visits (28%) and facility deliveries (38%). The low rates of induction and caesarean section point to a very low proportion of the PTBs being due to iatrogenic causes.

In many other settings, both younger and older maternal age have been reported to be risk factors for preterm birth. [24-30] Being from Muslim caste was positively associated with preterm as compared to Brahmin/Chhetri, which constitutes the major caste in Nepal. Caste/religion is a social construction, and studies in different places have shown that women in minor caste/race/color have higher risk of preterm births. [31-33] It significantly matters what position an individual holds within a society, with regards to occurrence of diseases and also their unequal distribution.[34-36]. First pregnancy (primipara) has been shown to be associated with spontaneous preterm birth in other studies. A study in France showed that primipara as compared to parity 2-3 increased the risk of preterm birth by 1.8 times.[37] Another study in the USA showed that being primipara as compared to multipara increased the risk of very preterm and extremely preterm birth, with the highest risk of 1.37 times for extremely preterm birth.[38] Meta-analysis done using 14 cohort studies from LMICs [39] and a study from sub-saharan African countries [40] also show that primiparity is associated with increased odds of preterm birth. Primipara is a risk factor for hypertensive disorders of pregnancy (HDP), which increases the risk of preterm birth.[41] Our study did not show interpregnancy interval to be the risk factor for spontaneous preterm birth. However, other

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3 studies on relationships between interpregnancy interval and preterm birth consistently showed  
4 that shorter interpregnancy intervals increase the risk of preterm births. However, the intervals  
5 used were not uniform across studies. One study found that, compared to an IPI of 18–23  
6 months, IPIs <3, 3–5, and 6–12 months had higher risks for preterm birth.[42] Another study  
7 with median IPI of 36 months showed that, compared to an IPI of 24–36 months, an IPI of  
8 <24 months was associated with preterm delivery.[43] Different studies corroborate our  
9 finding that multiple births are a risk factor for preterm birth. [18, 44, 45] Similar to our study,  
10 others also found male children at higher risk of being preterm[46-48], but a study in Nepal  
11 found that female children had a higher risk of being preterm.[18] This study in Nepal enrolled  
12 live births in a hospital setting, and had almost half the prevalence of our study. [18] They  
13 could have missed more males that had preterm births at home or on the way to a facility.  
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24 Different studies in Nepal [18] and outside of Nepal [49-51] have also shown that higher  
25 education of mothers decreases the risk of preterm births. Higher education of mothers can lead  
26 to increased knowledge and awareness regarding pregnancy-related care and thus decrease  
27 adverse outcomes of pregnancy. We found greater maternal height to be protective for  
28 spontaneous preterm birth, similar to the findings from a meta-analysis done using 12 cohort  
29 studies from LMICs. [52] .We found that women in the richer wealth quintile had a lower risk  
30 of spontaneous preterm births. Having higher household economic status probably does not  
31 directly affect the gestational age at outcome, instead, it probably is mediated by factors like  
32 nutrition, physically demanding work during pregnancy, type of care at home, stress level and  
33 other psychological factors.[53]  
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43 Pregnancy-varying morbidities that significantly decreased the risk of preterm birth in our  
44 analysis were respiratory problems in the 3<sup>rd</sup> trimester; and poor appetite, nausea and vomiting  
45 in the 2<sup>nd</sup> trimester, and the 3<sup>rd</sup> trimester. On segregating the symptoms within respiratory  
46 problems , we found that it was the persistent cough in the 3<sup>rd</sup> trimester that decreased the risk  
47 of preterm. A similar relationship was found between persistent cough and Large for  
48 Gestational Age (LGA) in another study done using the same data as ours. [54] However, we  
49 could not find any such association in the previous literature. The association might be due to  
50 some unmeasured confounders. Or it could be that women with persistent cough in the  
51 3<sup>rd</sup> trimester made more frequent check-up visits. We saw that 40% of women with persistent  
52 cough in the 3<sup>rd</sup> trimester sought treatment for cough, and almost all had sought treatment  
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3 more than once. The pathogenesis of nausea and vomiting in pregnancy is not very clear, but  
4 it is broadly accepted to be multifactorial, with the involvement of genetic, endocrine, and  
5 gastrointestinal factors. [55] Our findings corroborate with previous findings that nausea and  
6 vomiting is associated with reduced risk of preterm birth. [56-59] Specifying by trimesters, a  
7 study by Wallin et. al. in Nepal showed similar findings - poor appetite, nausea and vomiting  
8 in first trimester was not significantly associated with spontaneous preterm births, but having  
9 these symptoms in the 2<sup>nd</sup> trimester decreased the risk of spontaneous preterm by 25%. [60]  
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17 Pregnancy-varying morbidities that significantly increased the risk of spontaneous preterm  
18 birth were vaginal bleeding, swelling of hands and face, high diastolic and systolic BP, all in  
19 the 3<sup>rd</sup> trimester. Other studies show similar results for vaginal bleeding. Vaginal bleeding is  
20 associated with fetal exposure to oral pathogens, which thereby increases the risk of  
21 spontaneous preterm birth, however, whether bleeding is the cause or result of fetal exposure  
22 to oral pathogens is not clear. [61] A prospective cohort study, separating first and second  
23 trimesters showed that vaginal bleeding in both trimesters increased the risk of preterm birth  
24 by 3.6 times, while bleeding in the second trimester only, was not associated with preterm  
25 birth. [62] A systematic review using 23 studies showed that bleeding in early pregnancy  
26 increased the risk of preterm births. [63] A study in China showed that vaginal bleeding in the  
27 first-trimester increased the risk of preterm births, and the severity, duration and initial timing  
28 of vaginal bleeding had different effects on the severity of preterm births. [61] Due to the low  
29 enrollment of women in the 1<sup>st</sup> trimester, we could not look at the association of vaginal  
30 bleeding in the 1<sup>st</sup> trimester with spontaneous preterm birth. However, all of the above  
31 information indicates that vaginal bleeding can be an important predictor of spontaneous  
32 preterm birth and health care workers should recommend appropriate interventions for women  
33 if they present with vaginal bleeding (such as more frequent follow up or referral for higher  
34 level care).  
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50 Other studies on blood pressure during pregnancy have also shown that a rise in systolic BP  
51 (over 30 mm Hg) or diastolic BP (over 15mm Hg), from early pregnancy to the mid third  
52 trimester significantly increased the risk of spontaneous preterm birth by 2 to 3 times. [64]  
53 Another study showed that an increase in 10 mm Hg in diastolic BP increased the risk of  
54 preterm birth by 29%. [65] These indicate the importance of measuring BP during the 3<sup>rd</sup>  
55 trimester. High BP in the 3<sup>rd</sup> trimester is an indicator of pre-eclampsia/eclampsia and can  
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3 predict preterm birth. Measuring BP frequently and monitoring the rise and cause of increased  
4 BP is important for predicting spontaneous preterm birth.  
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8 For maternal weight, higher weight gain from the 2nd to the 3rd trimester decreased the risk of  
9 spontaneous preterm birth. This is consistent with a study done outside Nepal, which showed  
10 that very low weight gain was strongly associated with very preterm delivery, and that this  
11 varied by pre-pregnancy BMI, where underweight women had the highest association and very  
12 obese women had lowest association with preterm.[66] Our study was conducted in a non-  
13 obese and undernourished population. We do not have pre-pregnancy BMI, so we looked at  
14 the mean BMI in the first trimester. Though the first trimester represents less than half of the  
15 pregnancies in the study, it hints at undernutrition in the population. The mean BMI was 19.1  
16 kg/m<sup>2</sup>, and 37% had BMI less than 18.5 kg/m<sup>2</sup>. So, less maternal weight gain in such  
17 population can pose a risk to spontaneous preterm births. Given spontaneous preterm births  
18 have shorter gestation, the increase in weight gain will likely be less because there is less time  
19 to increase weight, especially in the third trimester, when much of the gestational weight is  
20 gained.  
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### 34 **Strengths and Limitations**

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36 This was a large population-based study that was generally representative of the rural Terai  
37 region of Nepal. Multiple variables were collected, including socioeconomic, demographic,  
38 pregnancy history, and monthly morbidity in pregnancy that could be examined as risk factors  
39 for spontaneous preterm birth. Although there was some missing data in regression analyses, a  
40 comparison of those with and without missing data did not show large differences in risk factor  
41 prevalence. However, those missing data had higher prevalence of preterm birth. It is possible  
42 that if women with missing data were included in the regression, we may have seen stronger  
43 associations but the potential bias of these differences is unclear. Gestational age (GA) at birth  
44 was measured using date of last menstrual period (LMP) as usually done in the LMICs rather  
45 than by ultrasound. However, as LMP was asked at enrollment which was generally early in  
46 pregnancy, there is less recall bias than LMP recalled at delivery or late in pregnancy. Using  
47 the same method as we used to obtain LMP, Gernand et al. found that LMP based estimates of  
48 GA in rural Bangladesh were a mean 2.8 days longer than what was obtained on ultrasound.  
49 [67] We therefore believe that this is probably not a significant limitation. Women were  
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3 followed prospectively at monthly intervals to reduce recall bias about pregnancy morbidities  
4 and symptoms. In order to reduce misclassification of stillbirths and live births, women were  
5 asked whether the infant moved, breathed or cried after birth.  
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10 Some variables associated with increased risk of spontaneous preterm births in previous  
11 studies, for example, a prior pregnancy ending in a preterm birth, gestational diabetes , maternal  
12 anemia and pre-pregnancy maternal nutritional status were not measured in the main trial.  
13 However, other important morbidity variables were measured and used in the analysis. We  
14 believe these risk factors are likely generalizable for similar populations in South Asia.  
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## 21 **CONCLUSION**

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24 Preterm birth is a leading risk factor for neonatal and under-5 mortality and morbidity  
25 worldwide. To reduce neonatal mortality, preventing preterm births can be a vital step. Some  
26 of the risk factors from our study are amenable to antenatal interventions but many others need  
27 more understanding of the underlying causal mechanisms. Maternal education and awareness  
28 can play a role in the long term, while good quality antenatal care, as suggested by the new  
29 WHO recommendation of 8 contacts during pregnancy, may help reduce some PTBs. Future  
30 research should focus on basic research involving the field of ‘omics’ using biological samples  
31 and implementation research to improve antenatal care and maternal nutrition.  
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## 39 **OTHER INFORMATION**

### 40 **Authors’ contribution:**

41  
42 SS, EH, DM, SZ, REB and JK conceptualized and designed the analysis. SS conducted the  
43 analysis and wrote the manuscript. LCM, JMT, SKK, SLC and JK were investigators in the  
44 parent trial. All authors reviewed results, analysis, discussed interpretations, and contributed  
45 to development and revision of the manuscript.  
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### 52 **Competing interests:**

53 The authors declare that they have no competing interests.  
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**Availability of data and materials:**

No data are available.

**Consent for publication:**

No individual information including data, images and video are included in this manuscript.

**Ethics approval and consent to participate:**

NOMS was approved by the institutional review board (IRB) of the Johns Hopkins Bloomberg School of Public Health in the USA and by the IRB of the Institute of Medicine, Tribhuvan University, Kathmandu, Nepal. This analysis of secondary data was considered exempt by the Johns Hopkins Bloomberg School of Public Health institutional review board (IRB) (FWA00000287). Verbal consent was obtained from women for their participation and their infants for the primary data collection.

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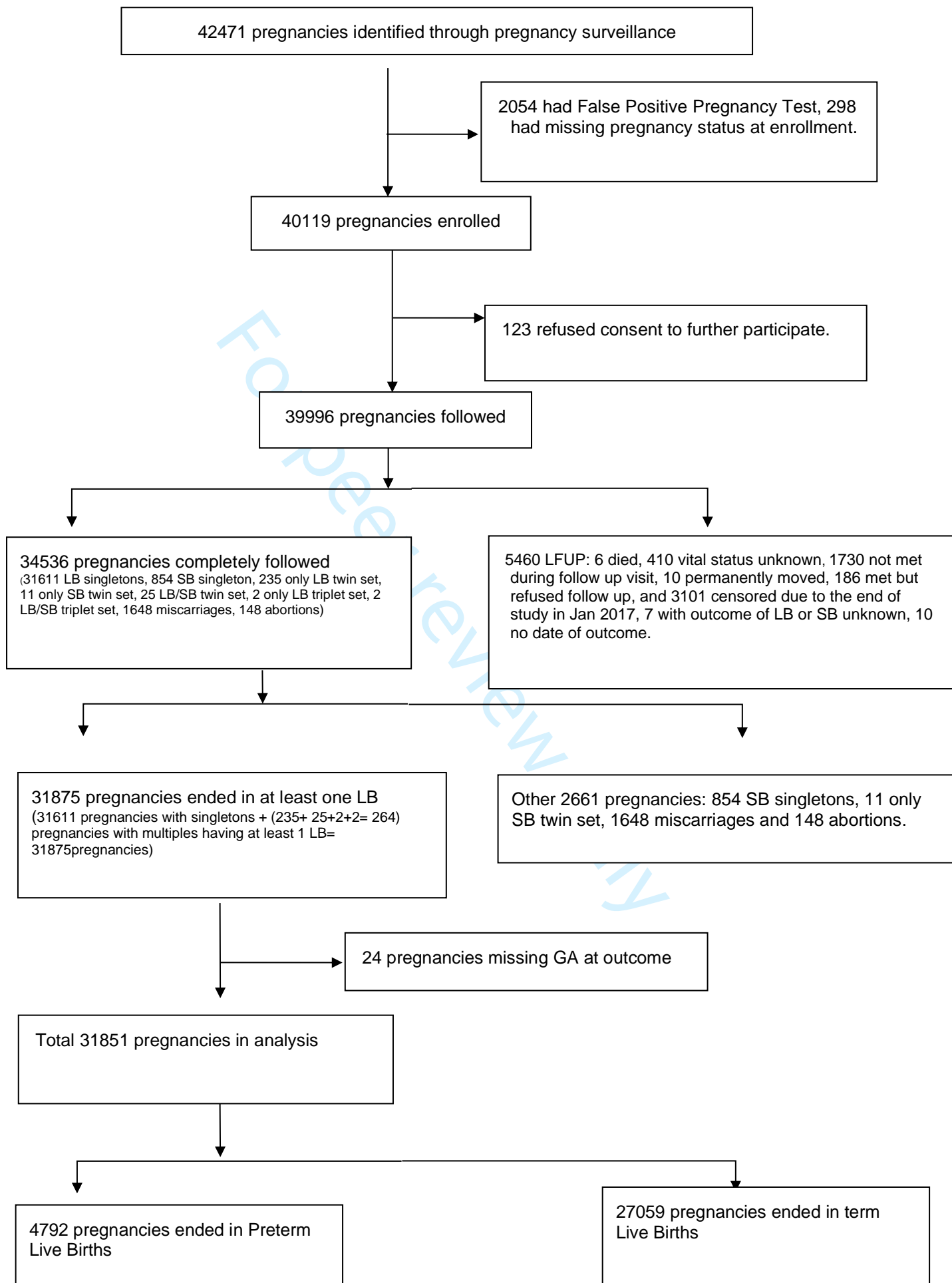
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Figure 1- Flow Diagram of Participants

For peer review only

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**Figure 1: Flow Diagram for Participants**

## SUPPLEMENTARY TABLES

Table S1. Comparing Pregnancy non-varying Variables by pregnancies Included and Excluded in the Regression Analysis

| Variables  | Categories                  | Total             | Included in regression | Excluded in regression | p-value |
|--|-----------------------------|-------------------|------------------------|------------------------|---------|
|  |                             | N=30,758<br>N (%) | N=21,297<br>N (%)      | N=9,461<br>N (%)       |         |
| Maternal Age at LMP                              | 18 to 35                    | 25,300 (82.3)     | 17,683 (83.0)          | 7,617 (80.5)           | <0.001  |
|  | Less than 18                | 4,792 (15.6)      | 3,169 (14.9)           | 1,623 (17.2)           |         |
|  | More than 35                | 666 ( 2.2)        | 445 ( 2.1)             | 221 ( 2.3)             |         |
| Caste/Ethnicity Categories                       | Brahmin and Chhetri         | 879 ( 2.9)        | 661 ( 3.1)             | 218 ( 2.3)             | <0.001  |
|  | Vaishya                     | 22,104 (71.9)     | 15,412 (72.4)          | 6,692 (70.7)           |         |
|  | Shudra                      | 4,826 (15.7)      | 3,392 (15.9)           | 1,434 (15.2)           |         |
|  | Muslim and others           | 2,919 ( 9.5)      | 1,832 ( 8.6)           | 1,087 (11.5)           |         |
|  | Missing                     | 30 ( 0.1)         | 0 ( 0.0)               | 30 ( 0.3)              |         |
| Mother's Education                               | No schooling                | 20,891 (67.9)     | 14,561 (68.4)          | 6,330 (66.9)           | 0.032   |
|  | 1 to 5 years                | 2,613 ( 8.5)      | 1,819 ( 8.5)           | 794 ( 8.4)             |         |
|  | More than 5 years           | 7,224 (23.5)      | 4,917 (23.1)           | 2,307 (24.4)           |         |
|  | Missing                     | 30 ( 0.1)         | 0 ( 0.0)               | 30 ( 0.3)              |         |
| Quintiles of Wealth                              | Poorest                     | 6,354 (20.7)      | 4,414 (20.7)           | 1,940 (20.5)           | 0.004   |
|  | Poorer                      | 6,210 (20.2)      | 4,386 (20.6)           | 1,824 (19.3)           |         |
|  | Middle                      | 6,152 (20.0)      | 4,289 (20.1)           | 1,863 (19.7)           |         |
|  | Richer                      | 6,036 (19.6)      | 4,172 (19.6)           | 1,864 (19.7)           |         |
|  | Richest                     | 5,985 (19.5)      | 4,036 (19.0)           | 1,949 (20.6)           |         |
|  | Missing                     | 21 ( 0.1)         | 0 ( 0.0)               | 21 ( 0.2)              |         |
| Maternal Height (centimeter)                     | <145                        | 4,510 (14.7)      | 3,193 (15.0)           | 1,317 (13.9)           | 0.042   |
|  | 145-<150                    | 9,227 (30.0)      | 6,413 (30.1)           | 2,814 (29.7)           |         |
|  | >=150                       | 16,974 (55.2)     | 11,691 (54.9)          | 5,283 (55.8)           |         |
|  | Missing                     | 47 ( 0.2)         | 0 ( 0.0)               | 47 ( 0.5)              |         |
| Parity including both LB and SB, at Enrollment   | Parity 1 to 4               | 19,805 (64.4)     | 14,137 (66.4)          | 5,668 (59.9)           | <0.001  |
|  | More than 4                 | 1,351 ( 4.4)      | 875 ( 4.1)             | 476 ( 5.0)             |         |
|  | Prior Pregnant but parity 0 | 723 ( 2.4)        | 515 ( 2.4)             | 208 ( 2.2)             |         |
|  | No Prior Pregnant           | 8,717 (28.3)      | 5,770 (27.1)           | 2,947 (31.1)           |         |
|  | Missing                     | 162 ( 0.5)        | 0 ( 0.0)               | 162 ( 1.7)             |         |
| Interpregnancy Interval based on maternal recall | 18 to 36 months             | 7,723 (25.1)      | 5,540 (26.0)           | 2,183 (23.1)           | <0.001  |
|  | Less than 18 months         | 11,201 (36.4)     | 7,693 (36.1)           | 3,508 (37.1)           |         |
|  | More than 36 months         | 3,106 (10.1)      | 2,294 (10.8)           | 812 ( 8.6)             |         |
|  | No Prior Pregnancy          | 8,717 (28.3)      | 5,770 (27.1)           | 2,947 (31.1)           |         |
|  | Missing                     | 11 ( 0.0)         | 0 ( 0.0)               | 11 ( 0.1)              |         |
| Any deaths among Prior LB                        | Prior LB but not died       | 17,089 (55.6)     | 12,273 (57.6)          | 4,816 (50.9)           | <0.001  |
|  | Prior LB died               | 3,518 (11.4)      | 2,555 (12.0)           | 963 (10.2)             |         |
|  | Prior Pregnancy but no LB   | 980 ( 3.2)        | 699 ( 3.3)             | 281 ( 3.0)             |         |
|  | No prior pregnancy          | 8,717 (28.3)      | 5,770 (27.1)           | 2,947 (31.1)           |         |
|  | Missing                     | 454 ( 1.5)        | 0 ( 0.0)               | 454 ( 4.8)             |         |
| Any prior pregnancy ended in SB                  | Prior pregnancy but no SB   | 20,736 (67.4)     | 14,704 (69.0)          | 6,032 (63.8)           | <0.001  |

| Variables                                       | Categories                         | Total           | Included in regression | Excluded in regression | p-value |
|---|------------------------------------|-----------------|------------------------|------------------------|---------|
|   |                                    | <b>N=30,758</b> | <b>N=21,297</b>        | <b>N=9,461</b>         |         |
|   | Prior SB                           | 1,291 ( 4.2)    | 815 ( 3.8)             | 476 ( 5.0)             |         |
|   | No prior pregnancy                 | 8,717 (28.3)    | 5,770 (27.1)           | 2,947 (31.1)           |         |
|   | Missing                            | 14 ( 0.0)       | 8 ( 0.0)               | 6 ( 0.1)               |         |
| Any prior pregnancy ended in miscarriage?       | Prior pregnancy but no miscarriage | 18,554 (60.3)   | 12,959 (60.8)          | 5,595 (59.1)           | <0.001  |
|   | Prior miscarriage                  | 3,478 (11.3)    | 2,565 (12.0)           | 913 ( 9.7)             |         |
|   | No prior pregnancy                 | 8,717 (28.3)    | 5,770 (27.1)           | 2,947 (31.1)           |         |
|   | Missing                            | 9 ( 0.0)        | 3 ( 0.0)               | 6 ( 0.1)               |         |
| Any prior pregnancy ended in multiples?         | Prior pregnancy but no multiples   | 21,735 (70.7)   | 15,383 (72.2)          | 6,352 (67.1)           | <0.001  |
|   | Prior multiples                    | 286 ( 0.9)      | 135 ( 0.6)             | 151 ( 1.6)             |         |
|   | No prior pregnancy                 | 8,717 (28.3)    | 5,770 (27.1)           | 2,947 (31.1)           |         |
|   | Missing                            | 20 ( 0.1)       | 9 ( 0.0)               | 11 ( 0.1)              |         |
| Number of ANC visits                            | No visit                           | 5,431 (17.7)    | 3,788 (17.8)           | 1,643 (17.4)           | <0.001  |
|   | 1 visit                            | 4,047 (13.2)    | 2,836 (13.3)           | 1,211 (12.8)           |         |
|   | 2-3 visit                          | 9,443 (30.7)    | 6,809 (32.0)           | 2,634 (27.8)           |         |
|   | 4 or more                          | 8,342 (27.1)    | 6,532 (30.7)           | 1,810 (19.1)           |         |
|   | Missing                            | 3,495 (11.4)    | 1,332 ( 6.3)           | 2,163 (22.9)           |         |
| Place of Delivery                               | Home/Maiti                         | 15,669 (50.9)   | 11,348 (53.3)          | 4,321 (45.7)           | 0.002   |
|   | HP/Clinic/Hospital                 | 11,038 (35.9)   | 8,210 (38.6)           | 2,828 (29.9)           |         |
|   | Way to Facility/Outdoors           | 602 ( 2.0)      | 439 ( 2.1)             | 163 ( 1.7)             |         |
|   | Missing                            | 3,449 (11.2)    | 1,300 ( 6.1)           | 2,149 (22.7)           |         |
| Bidi or tobacco use in pregnancy                | No                                 | 30,410 (98.9)   | 21,060 (98.9)          | 9,350 (98.8)           | 0.64    |
|   | Yes                                | 348 ( 1.1)      | 237 ( 1.1)             | 111 ( 1.2)             |         |
| Alcohol use (jaard or rakshi) in pregnancy?     | No                                 | 30,665 (99.7)   | 21,230 (99.7)          | 9,435 (99.7)           | 0.56    |
|   | Yes                                | 93 ( 0.3)       | 67 ( 0.3)              | 26 ( 0.3)              |         |
| Multiple Birth                                  | Singleton                          | 30,508 (99.2)   | 21,147 (99.3)          | 9,361 (98.9)           | 0.001   |
|   | Twin/Triplet                       | 250 ( 0.8)      | 150 ( 0.7)             | 100 ( 1.1)             |         |
| Sex of the child                                | Female                             | 14,673 (47.7)   | 10,178 (47.8)          | 4,495 (47.5)           | 0.004   |
|   | Male                               | 15,736 (51.2)   | 10,969 (51.5)          | 4,767 (50.4)           |         |
|   | Twin/Triplet                       | 250 ( 0.8)      | 150 ( 0.7)             | 100 ( 1.1)             |         |
|   | Missing                            | 99 ( 0.3)       | 0 ( 0.0)               | 99 ( 1.0)              |         |
| Preterm Birth                                   | Term                               | 26,130 (85.0)   | 18,363 (86.2)          | 7,767 (82.1)           | <0.001  |
|   | Preterm                            | 4,628 (15.0)    | 2,934 (13.8)           | 1,694 (17.9)           |         |
| Gestational Age at outcome in weeks (Mean (SD)) |                                    | 39.4 (3.4)      | 39.5 (2.7)             | 39.2 (4.6)             | <0.001  |

Table S2-Comparing the Adjusted Risk Ratios for associations between risk factors and spontaneous preterm birth in different models

| Name of Variables                              | Categories                  | Model 1<br>Unadjusted Model<br><br>Risk Ratio<br>(95% CI) | Model 2<br>Adjusted Model<br>without<br>ANC/Place of<br>Delivery<br>(N=21,297)<br><br>Risk Ratio<br>(95% CI) | Model 3<br>Adjusted- Added<br>ANC<br>(N=19,965)<br><br>Risk Ratio<br>(95% CI) | Model 4<br>Adjusted- Added<br>ANC and Place<br>of Delivery<br>(N=19,964)<br><br>Risk Ratio<br>(95% CI) |
|--|-----------------------------|---|--|---|--|
| Maternal Age at LMP                            | 18 to 35                    | 1.00 [1.00,1.00]  | 1.00 [1.00,1.00]   | 1.00 [1.00,1.00]  | 1.00 [1.00,1.00]   |
|  | Less than 18                | 1.19*** [1.11,1.28]                                       | 1.13* [1.02,1.26]  | 1.11 [1.00,1.24]  | 1.11* [1.00,1.24]  |
|  | More than 35                | 1.57*** [1.36,1.81]                                       | 1.22 [0.98,1.51]   | 1.20 [0.97,1.49]  | 1.20 [0.97,1.49]   |
| Caste/Ethnicity Categories                     | Brahmin and Chhetri         | 1.00 [1.00,1.00]  | 1.00 [1.00,1.00]   | 1.00 [1.00,1.00]  | 1.00 [1.00,1.00]   |
|  | Vaishya                     | 1.33** [1.09,1.62]  | 1.23 [0.95,1.59]   | 1.19 [0.92,1.54]  | 1.20 [0.92,1.54]   |
|  | Shudra                      | 1.55*** [1.26,1.90]                                       | 1.23 [0.94,1.62]   | 1.18 [0.90,1.55]  | 1.18 [0.90,1.55]   |
|  | Muslim and others           | 1.96*** [1.60,2.42]                                       | 1.53** [1.16,2.01]   | 1.53** [1.16,2.01]  | 1.53** [1.16,2.02]   |
| Mother's Years of Education                    | No schooling                | 1.00 [1.00,1.00]  | 1.00 [1.00,1.00]   | 1.00 [1.00,1.00]  | 1.00 [1.00,1.00]   |
|  | 1 to 5 years                | 0.86** [0.78,0.95]  | 0.91 [0.80,1.03]   | 0.95 [0.83,1.08]  | 0.95 [0.83,1.08]   |
|  | More than 5 years           | 0.71*** [0.66,0.76]                                       | 0.81*** [0.73,0.90]  | 0.85** [0.77,0.95]  | 0.85** [0.76,0.94]   |
| Quintiles of Wealth                            | Poorest                     | 1.00 [1.00,1.00]  | 1.00 [1.00,1.00]   | 1.00 [1.00,1.00]  | 1.00 [1.00,1.00]   |
|  | Poorer                      | 0.86*** [0.79,0.93]                                       | 0.90* [0.82,1.00]  | 0.91 [0.83,1.01]  | 0.91 [0.83,1.01]   |
|  | Middle                      | 0.89** [0.82,0.96]  | 0.95 [0.86,1.05]   | 0.98 [0.88,1.08]  | 0.97 [0.88,1.08]   |
|  | Richer                      | 0.73*** [0.67,0.79]                                       | 0.83** [0.74,0.93]   | 0.88* [0.78,0.98]   | 0.87* [0.78,0.98]  |
|  | Richest                     | 0.71*** [0.65,0.77]                                       | 0.88* [0.78,1.00]  | 0.91 [0.80,1.03]  | 0.90 [0.80,1.02]   |
| Mother's height(centimeter)                    | <145                        | 1.00 [1.00,1.00]  | 1.00 [1.00,1.00]   | 1.00 [1.00,1.00]  | 1.00 [1.00,1.00]   |
|  | 145-<150                    | 0.93 [0.86,1.01]  | 0.98 [0.88,1.08]   | 0.98 [0.89,1.09]  | 0.99 [0.89,1.09]   |
|  | >=150                       | 0.81*** [0.75,0.87]                                       | 0.89* [0.81,0.98]  | 0.90* [0.82,1.00]   | 0.91 [0.82,1.00]   |
| Parity including both LB and SB, at Enrollment | Parity 1 to 4               | 1.00 [1.00,1.00]  | 1.00 [1.00,1.00]   | 1.00 [1.00,1.00]  | 1.00 [1.00,1.00]   |
|  | More than 4                 | 1.32*** [1.17,1.48]                                       | 1.17 [0.99,1.37]   | 1.11 [0.95,1.31]  | 1.12 [0.95,1.31]   |
|  | Prior Pregnant but parity 0 | 1.02 [0.85,1.22]  | 0.92 [0.62,1.37]   | 1.12 [0.73,1.73]  | 1.11 [0.72,1.72]   |
|  | No Prior Pregnant           | 1.10** [1.04,1.17]  | 1.15** [1.04,1.28]   | 1.20** [1.07,1.34]  | 1.19** [1.07,1.33]   |
| Interpregnancy Intervals                       | 18 to 36 months             | 1.00 [1.00,1.00]  | 1.00 [1.00,1.00]   | 1.00 [1.00,1.00]  | 1.00 [1.00,1.00]   |
|  | Less than 18 months         | 1.07 [0.99,1.14]  | 1.08 [0.99,1.18]   | 1.09 [0.99,1.19]  | 1.09 [0.99,1.19]   |
|  | More than 36 months         | 0.98 [0.89,1.09]  | 0.90 [0.79,1.02]   | 0.93 [0.82,1.06]  | 0.93 [0.82,1.06]   |
|  | No Prior Pregnancy          | 1.11** [1.03,1.20]  | 1.00 [1.00,1.00]   | 1.00 [1.00,1.00]  | 1.00 [1.00,1.00]   |
| Any death among prior LB                       | Prior LB but not died       | 1.00 [1.00,1.00]  | 1.00 [1.00,1.00]   | 1.00 [1.00,1.00]  | 1.00 [1.00,1.00]   |
|  | Prior LB died               | 1.19*** [1.09,1.29]                                       | 1.07 [0.97,1.19]   | 1.07 [0.96,1.20]  | 1.07 [0.96,1.20]   |
|  | Prior Pregnancy but no LB   | 1.07 [0.92,1.25]  | 1.06 [0.75,1.49]   | 0.97 [0.66,1.41]  | 0.96 [0.66,1.41]   |
|  | No prior pregnancy          | 1.12*** [1.06,1.19]                                       |  |   |  |

| Name of Variables   | Categories                         | Model 1<br>Unadjusted Model | Model 2<br>Adjusted Model<br>without<br>ANC/Place of<br>Delivery<br>(N=21,297) | Model 3<br>Adjusted- Added<br>ANC<br>(N=19,965) | Model 4<br>Adjusted- Added<br>ANC and Place<br>of Delivery<br>(N=19,964) |
|---|------------------------------------|-----------------------------|--|---|--|
|   |                                    | Risk Ratio<br>(95%CI)       | Risk Ratio<br>(95%CI)  | Risk Ratio<br>(95%CI)                           | Risk Ratio<br>(95%CI)  |
| Any prior pregnancy ended in SB                             | Prior pregnancy but no SB          | 1.00 [1.00,1.00]            |  |   |  |
|   | Prior SB                           | 1.08 [0.94,1.23]            |  |   |  |
|   | No prior pregnancy                 | 1.08** [1.02,1.15]          |  |   |  |
| Any prior pregnancy ended in miscarriage                    | Prior pregnancy but no miscarriage | 1.00 [1.00,1.00]            |  |   |  |
|   | Prior miscarriage                  | 0.94 [0.86,1.03]            |  |   |  |
|   | No prior pregnancy                 | 1.07* [1.01,1.13]           |  |   |  |
| Any prior pregnancy ended in multiples                      | Prior pregnancy but no multiples   | 1.00 [1.00,1.00]            |  |   |  |
|   | Prior multiples                    | 1.14 [0.87,1.49]            |  |   |  |
|   | No prior pregnancy                 | 1.08** [1.02,1.14]          |  |   |  |
| Number of ANC Visits  | No visit                           | 1.00 [1.00,1.00]            |  | 1.00 [1.00,1.00]                                | 1.00 [1.00,1.00]   |
|   | 1 visit                            | 0.98 [0.89,1.07]            |  | 1.00 [0.90,1.12]                                | 1.00 [0.90,1.12]   |
|   | 2-3 visit                          | 0.92* [0.85,0.99]           |  | 0.94 [0.86,1.03]                                | 0.93 [0.85,1.02]   |
|   | 4 or more                          | 0.54*** [0.50,0.59]         |  | 0.64***<br>[0.57,0.71]                          | 0.62***<br>[0.56,0.70]   |
| Place of Delivery   | Home/Maiti                         | 1.00 [1.00,1.00]            |  |   | 1.00 [1.00,1.00]   |
|   | HP/Clinic/Hospital                 | 0.84*** [0.79,0.89]         |  |   | 1.04 [0.96,1.12]   |
|   | Way to Facility/Outdoors           | 1.28** [1.09,1.51]          |  |   | 1.23 [1.00,1.52]   |
| Multiple Birth  | Singleton                          | 1.00 [1.00,1.00]            | 1.00 [1.00,1.00]   | 1.00 [1.00,1.00]                                | 1.00 [1.00,1.00]   |
|   | Twin/Triplet                       | 3.92*** [3.52,4.38]         | 4.91***<br>[4.20,5.75]   | 4.97***<br>[4.25,5.82]                          | 4.96***<br>[4.24,5.81]   |
| Sex of the Child  | Female                             | 1.00 [1.00,1.00]            | 1.00 [1.00,1.00]   | 1.00 [1.00,1.00]                                | 1.00 [1.00,1.00]   |
|   | Male                               | 1.10*** [1.04,1.17]         | 1.10** [1.02,1.17]   | 1.08* [1.01,1.16]                               | 1.08* [1.01,1.16]  |
|   | Twin/Triplet                       | 4.13*** [3.69,4.63]         | 1.00 [1.00,1.00]   | 1.00 [1.00,1.00]                                | 1.00 [1.00,1.00]   |
| STI in at least one visit of 2nd trimester?                 | No                                 | 1.00 [1.00,1.00]            |  |   |  |
|   | Yes                                | 0.99 [0.92,1.07]            |  |   |  |
| STI in at least one visit of 3rd trimester?                 | No                                 | 1.00 [1.00,1.00]            |  |   |  |
|   | Yes                                | 1.01 [0.92,1.12]            |  |   |  |
| Respiratory Problem in at least one visit of 2nd trimester? | No                                 | 1.00 [1.00,1.00]            | 1.00 [1.00,1.00]   | 1.00 [1.00,1.00]                                | 1.00 [1.00,1.00]   |
|   | Yes                                | 1.00 [0.94,1.06]            | 1.08 [1.00,1.16]   | 1.09* [1.01,1.18]                               | 1.09* [1.01,1.18]  |
| Respiratory Problem in at least one visit of 3rd trimester? | No                                 | 1.00 [1.00,1.00]            | 1.00 [1.00,1.00]   | 1.00 [1.00,1.00]                                | 1.00 [1.00,1.00]   |
|   | Yes                                | 0.85*** [0.79,0.92]         | 0.86** [0.79,0.94]   | 0.86** [0.78,0.94]                              | 0.86** [0.78,0.94]   |
| GI Problem in at least one visit of 2nd trimester?          | No                                 | 1.00 [1.00,1.00]            |  |   |  |
|   | Yes                                | 1.08 [0.98,1.18]            |  |   |  |
| GI Problem in at least one visit of 3rd trimester?          | No                                 | 1.00 [1.00,1.00]            |  |   |  |
|   | Yes                                | 1.04 [0.94,1.16]            |  |   |  |

| Name of Variables  | Categories          | Model 1<br>Unadjusted Model | Model 2<br>Adjusted Model<br>without<br>ANC/Place of<br>Delivery<br>(N=21,297) | Model 3<br>Adjusted- Added<br>ANC<br>(N=19,965) | Model 4<br>Adjusted- Added<br>ANC and Place<br>of Delivery<br>(N=19,964) |
|--|---------------------|-----------------------------|--|---|--|
|  |                     | Risk Ratio<br>(95%CI)       | Risk Ratio<br>(95%CI)  | Risk Ratio<br>(95%CI)                           | Risk Ratio<br>(95%CI)  |
| Poor appetite, nausea & vomiting in at least one visit of 2nd trimester?   | No                  | 1.00 [1.00,1.00]            | 1.00 [1.00,1.00]   | 1.00 [1.00,1.00]                                | 1.00 [1.00,1.00]   |
|  | Yes                 | 0.81*** [0.77,0.86]         | 0.86***<br>[0.80,0.92]   | 0.88***<br>[0.82,0.94]                          | 0.88***<br>[0.81,0.94]   |
| Poor appetite, nausea & vomiting in at least one visit of 3rd trimester?   | No                  | 1.00 [1.00,1.00]            | 1.00 [1.00,1.00]   | 1.00 [1.00,1.00]                                | 1.00 [1.00,1.00]   |
|  | Yes                 | 0.88** [0.82,0.95]          | 0.86***<br>[0.79,0.94]   | 0.87** [0.79,0.95]                              | 0.87** [0.79,0.95]   |
| Vaginal Bleeding in at least one visit of 2nd trimester?                   | No                  | 1.00 [1.00,1.00]            | 1.00 [1.00,1.00]   | 1.00 [1.00,1.00]                                | 1.00 [1.00,1.00]   |
|  | Yes                 | 0.91 [0.71,1.17]            | 0.84 [0.62,1.16]   | 0.83 [0.60,1.14]                                | 0.83 [0.60,1.15]   |
| Vaginal Bleeding in at least one visit of 3rd trimester?                   | No                  | 1.00 [1.00,1.00]            | 1.00 [1.00,1.00]   | 1.00 [1.00,1.00]                                | 1.00 [1.00,1.00]   |
|  | Yes                 | 1.44* [1.05,1.98]           | 1.53* [1.08,2.18]  | 1.49* [1.04,2.13]                               | 1.50* [1.04,2.15]  |
| Swelling in at least one visit of 2nd trimester?                           | No                  | 1.00 [1.00,1.00]            | 1.00 [1.00,1.00]   | 1.00 [1.00,1.00]                                | 1.00 [1.00,1.00]   |
|  | Yes                 | 1.32*** [1.12,1.55]         | 1.19 [0.98,1.46]   | 1.21 [0.98,1.48]                                | 1.21 [0.99,1.48]   |
| Swelling in at least one visit of 3rd trimester?                           | No                  | 1.00 [1.00,1.00]            | 1.00 [1.00,1.00]   | 1.00 [1.00,1.00]                                | 1.00 [1.00,1.00]   |
|  | Yes                 | 1.25** [1.09,1.44]          | 1.37***<br>[1.17,1.60]   | 1.36***<br>[1.15,1.60]                          | 1.36***<br>[1.15,1.60]   |
| High Systolic BP in one visit of 2nd trimester?                            | Normal Systolic BP  | 1.00 [1.00,1.00]            | 1.00 [1.00,1.00]   | 1.00 [1.00,1.00]                                | 1.00 [1.00,1.00]   |
|  | High Systolic BP    | 0.89 [0.59,1.34]            | 0.67 [0.40,1.12]   | 0.65 [0.39,1.09]                                | 0.65 [0.39,1.09]   |
| High Systolic BP in one visit of 3rd trimester?                            | Normal Systolic BP  | 1.00 [1.00,1.00]            | 1.00 [1.00,1.00]   | 1.00 [1.00,1.00]                                | 1.00 [1.00,1.00]   |
|  | High Systolic BP    | 1.92*** [1.52,2.41]         | 1.47* [1.08,2.01]  | 1.49* [1.08,2.07]                               | 1.49* [1.07,2.07]  |
| High Diastolic BP in one visit of 2nd trimester?                           | Normal diastolic BP | 1.00 [1.00,1.00]            | 1.00 [1.00,1.00]   | 1.00 [1.00,1.00]                                | 1.00 [1.00,1.00]   |
|  | High diastolic BP   | 1.34** [1.12,1.60]          | 1.09 [0.85,1.40]   | 1.06 [0.82,1.37]                                | 1.06 [0.82,1.38]   |
| High Diastolic BP in one visit of 3rd trimester?                           | Normal diastolic BP | 1.00 [1.00,1.00]            | 1.00 [1.00,1.00]   | 1.00 [1.00,1.00]                                | 1.00 [1.00,1.00]   |
|  | High diastolic BP   | 1.57*** [1.37,1.80]         | 1.41***<br>[1.17,1.70]   | 1.35** [1.12,1.64]                              | 1.35** [1.12,1.64]   |
| Average weight in 3rd trimester minus Average weight in 2nd trimester (kg) |                     | 0.88*** [0.87,0.90]         | 0.89***<br>[0.87,0.90]   | 0.89***<br>[0.87,0.90]                          | 0.89***<br>[0.87,0.90]   |

\*  $p < 0.05$ , \*\*  $p < 0.01$ , \*\*\*  $p < 0.001$

# BMJ Open

## Prevalence and Predictors of Spontaneous Preterm Births in Nepal- Findings from a prospective, population-based pregnancy cohort in rural Nepal: A secondary data analysis

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3 **Prevalence and Predictors of Spontaneous Preterm Births in Nepal- Findings from a**  
4 **prospective, population-based pregnancy cohort in rural Nepal: A secondary data**  
5 **analysis**  
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## ABSTRACT

### Objective

Preterm birth can have short and long-term complications for a child. Socioeconomic factors and pregnancy-related morbidities may be important to predict and prevent preterm births in low-resource settings. The objective of our study was to find prevalence and predictors of spontaneous preterm birth in rural Nepal.

### Design

This is a secondary observational analysis of trial data (registration number NCT01177111)

### Setting

Rural Sarlahi district, Nepal

### Participants

40,119 pregnant women enrolled from September 9, 2010, to Jan 16, 2017

### Outcome Measures

The outcome variable is spontaneous preterm birth. Generalized Estimating Equations (GEE) Poisson regression with robust variance was fitted to present effect estimates as risk ratios.

### Result

The prevalence of spontaneous preterm birth was 14.5% (0.5% non-spontaneous). Characteristics not varying in pregnancy associated with increased risk of preterm birth were maternal age less than 18 (ARR=1.13, 95% CI: 1.02-1.26); being Muslim (1.53, 1.16-2.01); first pregnancy (1.15, 1.04-1.28); multiple birth (4.91, 4.20-5.75) and male child (1.10, 1.02-1.17). Those associated with decreased risk were maternal education >5 years (0.81, 0.73-0.90); maternal height  $\geq 150$  cm (0.89, 0.81-0.98) and being from wealthier families (0.83, 0.74-0.93). Pregnancy related morbidities associated with increased risk of preterm birth were vaginal bleeding (1.53, 1.08-2.18); swelling (1.37, 1.17-1.60); high systolic BP (1.47, 1.08-2.01) and high diastolic BP (1.41, 1.17-1.70) in the 3<sup>rd</sup> trimester. Those associated with decreased risk were respiratory problem in the 3<sup>rd</sup> trimester (0.86, 0.79-0.94); and having poor appetite, nausea and vomiting in 2<sup>nd</sup> trimester (0.86, 0.80-0.92) and 3<sup>rd</sup> trimester (0.86, 0.79-0.94); and higher weight gain from 2<sup>nd</sup> to 3<sup>rd</sup> trimester (0.89, 0.87-0.90).

### Conclusion

The prevalence of preterm is high in rural Nepal. Interventions that increase maternal education may play a role. Monitoring morbidities during antenatal care to intervene to reduce them through an effective health system may help reduce preterm.

## STRENGTHS AND LIMITATIONS OF THIS STUDY

- This is a large population-based study that allows for analysis of rare and common risk factors for a relatively rare outcome (preterm).
- Previous studies on preterm birth in Nepal were hospital-based, enrolled women during delivery and have explored only the women's socio-demographic factors associated with preterm birth, whereas our study is population-based, enrolls women from earlier in pregnancy, follows them monthly, and has explored symptoms and morbidities variables that change through pregnancy.
- Gestational age (GA) at outcome has been measured using date of last menstrual period (LMP) as usually done in LMICs, however, as LMP was asked at enrollment that was generally early in pregnancy, there is less recall bias than LMP recalled at delivery or late in pregnancy.
- Missing data for second trimester morbidities due to late enrollment of some women in pregnancy is a limitation, but comparison of sociodemographic characteristics suggest limited potential for biases due to this limitation.

## INTRODUCTION:

Preterm birth (PTB) is defined as a birth occurring before 37 completed gestational weeks or fewer than 259 days from a woman's last menstrual period (LMP).[1] In 2010, the global prevalence of preterm birth estimated in 92 countries was 11.1% (95% CI: 9.1%-13.4%), ranging from about 5% in some European countries to 18% in some African countries.[2] Sixty percent of these PTBs occurred in Sub-Saharan Africa and South Asia.[2] Complications of preterm birth was the leading cause of under-5 mortality and accounted for approximately 17.7 % of all under-5 mortality and 36.1% of neonatal mortality, according to the 2019 global estimates. [3] Eighty-one percent of the under-5 deaths from complications of preterm birth occurred in Asia and sub-Saharan Africa countries.[4]

Preterm births can have short and long-term consequences. Short-term consequences comprise increased risks of neonatal respiratory conditions, sepsis, neurological conditions, feeding difficulties, and visual and hearing problems.[5-7] As the child grows, long term consequences include more hospital admissions, poorer neurodevelopment outcomes, difficulties in learning, as well as behavioral and social-emotional problems.[8-10] At the family level, preterm birth can lead to significant economic and psychological difficulties, and at the national level, it leads to significant cost for the health system.[11, 12]

In Nepal, under-five mortality has dropped from 64 deaths to 39 deaths per 1000 live births (LB) from 2001 to 2016.[13-15] In the same period, neonatal mortality rate (NMR) has also steadily declined, (from 39 to 21 per 1,000 LB). [13-15]. Being an important determinant of neonatal mortality, preterm birth has become a greater contributor to under-5 mortality over time.[16] If we do not consider interventions to address preterm births, it would be difficult to achieve Nepal's Sustainable Development Goal (SDG) that aims to reduce the neonatal mortality to 12 per 1000 LB and under-5 mortality to 28 per 1000 LB by 2030.[17]

There are very few studies on the prevalence or risk factors for preterm birth in Nepal,[18, 19] and those that exist have limitations. First, those studies are hospital based. Women enrolled in hospitals during delivery may suffer from systematic recall bias, where women having a preterm birth might report differently from women with term births. Also, at the time of delivery, women might have recall issues in reporting their date of last menstrual period (LMP). Most important, enrolling at facilities has a selection bias, where the preterm births delivered

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3 at home or on-the-way to facilities are missed, possibly leading to underestimation of the  
4 prevalence and a different distribution of risk factors. Second, previous studies have included  
5 deliveries taken from urban tertiary hospitals in Nepal. Around 80% of the Nepalese population  
6 resides in rural areas[20] and do not have access to delivery services at tertiary centers.  
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8 Moreover, in rural areas, only 47% of deliveries are assisted by skilled birth attendants. [14]  
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10 So, the findings from those studies may not be representative of rural Nepal. Third, since the  
11 women's enrollment was during delivery, they looked at only risk factors that did not vary in  
12 pregnancy and did not analyze changing symptoms, behaviors, and maternal weight gain  
13 throughout pregnancy. Some of these symptoms may be indicative of conditions that can be  
14 addressed by antenatal care. The objective of our study was to estimate the prevalence and  
15 identify predictors/risk factors of spontaneous preterm births in rural Nepal. Understanding and  
16 addressing such risk factors is critical to addressing neonatal and child mortality and morbidity,  
17 particularly in resource-poor settings like Nepal.  
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## 26 **METHODS:**

### 27 **Study Design**

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32 This is a secondary data analysis with data taken from the Nepal Oil Massage Study (NOMS),  
33 which is a cluster-randomized community-based trial (ClinicalTrials.gov, NCT01177111) on  
34 the impact of sunflower seed oil versus standard of care mustard seed oil for neonatal massage  
35 on neonatal mortality and morbidity in rural Sarlahi district of Nepal. This study began by  
36 identifying married women of childbearing age (15 to 40 years) who consented to pregnancy  
37 surveillance. This involved following them every 5 weeks to see whether they became  
38 pregnant, based on a positive pregnancy test offered by the study team if a woman reported  
39 missing a period. If pregnant, they were consented and enrolled in the trial. During enrollment,  
40 demographic data, socioeconomic status, reproductive history, and date of last menstruation  
41 were collected. 123 women (0.3%) refused to be followed after enrollment. Those who  
42 consented were visited monthly by a field worker until the pregnancy outcome occurred or the  
43 study ended. During these monthly visits, field workers asked some basic questions about signs  
44 and symptoms of morbidity during the previous 30-day period. At these visits, women also had  
45 their weight and blood pressure (BP)/pulse measured, and body temperature recorded. Women  
46 reporting signs of morbidity and indicating that these signs were currently present were referred  
47 to the local health post or Primary Health Center. Women with fever or elevated blood pressure  
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3 as measured by study staff were similarly referred for care but continued to be included in the  
4 study.  
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8 As soon as possible after labor began or the baby was delivered, family members or neighbors  
9 notified the local female study worker of the birth. She notified a specially trained team who  
10 visited the mother and infant as soon after birth as possible. They measured infant weight and  
11 time of weight measurement after birth, determined sex of the newborn and whether the baby  
12 was a singleton or multiple birth.  
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### 17 **Setting and Participants**

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20 The study cohort consists of 40,119 pregnancies among married women of child-bearing age,  
21 living in 34 Village Development Committees (VDCs) of Sarlahi district, enrolled from  
22 September 9, 2010, to Jan 16, 2017, in the NOMS study. Pregnancies were followed monthly  
23 until delivery. Live births were categorized as term or preterm. Pregnancies ending in  
24 miscarriage, abortion and stillbirths (SB) were excluded from the analysis. Stillbirths were not  
25 included because the etiology of these may be quite different from those of preterm births.  
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### 32 **Variables**

#### 33 Outcome Variable

34  
35 The main outcome variable is spontaneous preterm birth among pregnancies that produced at  
36 least one live born infant, defined as pregnancies ending less than 259 gestational days from  
37 the first day of LMP date. Live births were based on women's self-report. They were asked if  
38 the baby moved, cried or breathed after birth. If they said "yes" to one or more of these, the  
39 birth was recorded as a live birth. For gestational age (GA), women were asked about their  
40 LMP during enrollment, and the GA at outcome was calculated as the difference between  
41 reported LMP and the date of the child's birth. Preterm births were classified as spontaneous  
42 or non-spontaneous (caesarian section or/and induction), and only spontaneous preterm births  
43 were included in the regression analysis.  
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#### 54 Independent Variables

55 Through literature review and expert opinion, certain factors were included in the analysis of  
56 predictors. [21] These can be categorized into pregnancy non-varying and pregnancy-varying  
57 variables. Pregnancy non-varying variables included sociodemographic, prior pregnancy  
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3 history, current pregnancy and child related variables that do not change during pregnancy.  
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5 Pregnancy-varying variables included signs and symptoms of morbidity in pregnancy, and  
6  
7 maternal weight.  
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10 Sociodemographic variables like maternal age at LMP, caste/religion, maternal education,  
11  
12 wealth quintile and maternal height were explored. Maternal age was categorized as less than  
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14 18, 18-35 and more than 35 years to assess the association of very young women and older  
15  
16 women with preterm births. Caste/religion of the mothers (Brahmin /Chhetri, Vaishya, Shudra,  
17  
18 Muslim and others) were used as per the caste category system in Nepal. [22] Maternal  
19  
20 education (No schooling, 1-5 years and more than 5 years); and maternal height (<145 cm,  
21  
22 145-<150 and  $\geq 150$ ) were used. Household wealth status was measured in quintiles based on  
23  
24 a standardized score using principal components analysis of household assets. [23]

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26 Prior pregnancy related variables like parity (1-4, more than 4, prior pregnant but not resulting  
27  
28 in live or still birth and no prior pregnant); interpregnancy interval (IPI) defined as the time  
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30 since the end of last pregnancy to the date of LMP of the current pregnancy, regardless of the  
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32 outcome (<18, 18-36, and >36 months); any prior live born child who died (No prior LB died  
33  
34 and Died); any prior pregnancy that ended in a SB (No prior SB and SB); any prior pregnancy  
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36 ending in miscarriage (No prior miscarriage and Miscarriage) ; and any prior pregnancy that  
37  
38 ended in multiples (No prior multiples and Multiples) were assessed.

39  
40 Current pregnancy related variables like tobacco intake (ever used any tobacco products during  
41  
42 this pregnancy- Yes and No), and alcohol intake (ever used alcohol during this pregnancy- Yes  
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44 and No) were assessed. Child-level variables like multiple birth (singleton and twin/triplet),  
45  
46 and sex of the child (male and female) were included. We used the category with the low risk  
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48 according to literature of similar settings, to be the reference group if there was no clear  
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50 hierarchy of risk (such as maternal age, caste) but selected the most at risk group for those  
51  
52 where a hierarchy existed (such as maternal education, wealth quintile, maternal height).

53  
54 Current pregnancy related variables like tobacco and alcohol intake were not included in the  
55  
56 regressions because rates of use were very low. Only 0.3% consumed alcohol and only 1.1%  
57  
58 used tobacco. Other current pregnancy related variables like number of antenatal care (ANC)  
59  
60 visits and place of delivery were shown in descriptive, but omitted from inferential analysis



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3 because in this setting, women with spontaneous preterm births could have missed the 4th ANC  
4 visit in the 9<sup>th</sup> month and preterm birth could be the cause of a lower number of visits. For place  
5 of delivery, spontaneous preterm births were more likely to be delivered at home or on the way  
6 to the facility, because many births in this environment are not planned to occur in a facility.  
7 However, we also included these variables in the multivariable regressions and provided these  
8 as supplemental analyses because ANC may be important in reducing preterm birth.  
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15 Symptoms of morbidity during pregnancy such as sexually transmitted diseases (STI),  
16 respiratory illness, gastrointestinal (GI) illness, poor appetite, nausea and vomiting, vaginal  
17 bleeding, swelling of hands or face, high systolic and diastolic blood pressure were assessed.  
18 All these variables were assessed in the 2<sup>nd</sup> and 3<sup>rd</sup> trimester, and so labelled as – Problem in  
19 at least one visit of the 2<sup>nd</sup> trimester- Yes or No, and Problem in at least one visit in the 3<sup>rd</sup>  
20 trimester- Yes or No. We did not include symptoms of morbidities in the 1<sup>st</sup> trimester because  
21 only 41% women were enrolled in the 1<sup>st</sup> trimester, and so 59% missed symptom information  
22 in the 1<sup>st</sup> trimester. Maternal weight gain was defined as the average weight in the 3<sup>rd</sup> trimester  
23 minus the average weight in the 2<sup>nd</sup> trimester. For measurement of these symptom variables,  
24 field workers asked if women had symptoms of morbidity at any time in the past 30 days, at  
25 each monthly visit during pregnancy. STI was defined as painful or burning urination, or foul  
26 smelling vaginal discharge. Respiratory illness was defined as persistent cough, or difficult or  
27 rapid breathing, or wheezing/grunting, or shortness of breath. GI illness was defined as watery  
28 stools (4 or more times in a day or blood or white mucus in the stool). Appetite related illness  
29 was defined as poor appetite, nausea or vomiting. Vaginal bleeding was defined as spots of  
30 blood from the vagina. Swelling was defined as swelling of hands and/or face. Foot/leg  
31 swelling was excluded since it is common during pregnancy and not indicative of underlying  
32 disease. BP measurements were categorized as high systolic BP if the systolic measurement  
33 was  $\geq 140$  mmHg, and high diastolic BP if diastolic measurement was  $\geq 90$  mmHg at any  
34 monthly visit within the 2<sup>nd</sup> or 3<sup>rd</sup> trimester.  
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## 51 **Statistical Methods**

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53 First, a descriptive analysis was done to show the frequencies of pregnancy non-varying  
54 variables (socio demographic, prior pregnancy related, current pregnancy and child related)  
55 and pregnancy varying variables (symptoms and maternal weight) by spontaneous preterm and  
56 term births. Second, bivariable GEE Poisson regression with robust variance was used to  
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3 examine associations between each risk factor and the outcome to get an unadjusted risk ratio.  
4 Since the prevalence of our outcome was more than 10%, we used Poisson regression with  
5 robust variance because we wanted to report associations as risk ratios. Third, multivariable  
6 GEE Poisson regression with robust variance was used including variables that were significant  
7 in the bivariable models, to get the adjusted risk ratios (ARR). GEE was used because in the  
8 study, 52% women had multiple pregnancies. Since our unit of analysis is pregnancy and  
9 pregnancies were nested within women, women's id variable was used as cluster for GEE  
10 modelling.  
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19 We included a larger number of potential risk factors to provide a general description of the  
20 study population but did not include all of these in the regression analysis. Some variables were  
21 highly correlated with each other (such as some reproductive history variables) and we chose  
22 just to include one rather than all, and for others, the prevalence was so low that we did not  
23 think helpful to include in the regression (for example, smoking and alcohol use). Some of the  
24 variables in the unadjusted analysis were not included in the regression because they were not  
25 statistically significant in the unadjusted analysis. For example, prior pregnancy ending in  
26 miscarriage, stillbirth or a prior multiple birth were not included (as these were highly  
27 correlated with each other and not statistically significant in crude models). We did include  
28 death of a prior livebirth, which was significant in the crude model.  
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38 The descriptive analysis had 31,851 pregnancies. In the regression analysis, we excluded the  
39 1093 pregnancies (3.4%) that ended in caesarian section, induction or both, which leaves  
40 30,758 for analysis. Then, 30.7% out of 30,758 ( 20.2% missing morbidity in 2<sup>nd</sup> trimester due  
41 to enrollment only in 3<sup>rd</sup> trimester, 9.4% missing morbidity in 3<sup>rd</sup> trimester and 1.1% missing  
42 other variables) were missing in the regression analysis, and so the final multivariable  
43 regression analysis excluded those 9,461 pregnancies, and consisted of 21,297 pregnancies.  
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### 49 **Patient and Public Involvement**

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52 Patients or the public were not involved in the design, or conduct, or reporting, or  
53 dissemination plans of this study.  
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## 56 **RESULTS:**

### 57 **Participants**

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3 The analytic population is 31,851 pregnancies that ended in at least one live birth and had  
4 information on gestational age at outcome. The detailed flow chart is given in Figure 1. Most  
5 women were enrolled in the 1<sup>st</sup> and 2<sup>nd</sup> trimester (41% each), followed by the 3<sup>rd</sup> trimester  
6 (18%). Overall, the mean gestational age at enrollment was 18 weeks. For 1<sup>st</sup>, 2<sup>nd</sup> and 3<sup>rd</sup>  
7 trimesters, the mean GA at enrollment were 9, 19 and 34 weeks respectively. 52% women  
8 (33% with two pregnancies, 14% with three pregnancies, 4% with four pregnancies and 1%  
9 with more than four pregnancies) contributed more than one pregnancy to the study.

## 16 **Descriptive Analysis**

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19 For pregnancy non-varying variables, as seen in Table 1, 15% of women were younger (less  
20 than 18) and 2% women were older (more than 35 years of age). 9% of women were Muslim  
21 caste/religion. Two thirds of women did not go to school, whereas only nearly one fourth had  
22 an education of more than five years. 15% of women had height <145cm. About a third (29%)  
23 of women had their first pregnancy in this study and 64% had one to four prior live or still  
24 births. Among those who had a previous pregnancy, 6% had prior still birth, 16% experienced  
25 miscarriage and 16% had a live birth that died, and only 1% had prior multiples. Half the  
26 women had an interpregnancy interval of less than 18 months, and 28% of women had four or  
27 more ANC visits. Half of the babies were born at home and 2% were born on the way to a  
28 facility or outdoors. Only 1.1% consumed tobacco and only 0.3% consumed alcohol during  
29 pregnancy. Half of the current pregnancies (51%) resulted in male children, and less than 1%  
30 resulted in multiple births. Only 3.4% of pregnancies underwent either caesarian section or  
31 induction or both.

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34 For pregnancy-varying variables, as seen in Table 2, poor appetite, nausea and vomiting was  
35 the most commonly reported symptom in both the second (39%) and third trimesters (20%);  
36 and vaginal bleeding was the least reported symptom (1.2% in the second and 0.6% in the third  
37 trimester). Very few women had high systolic blood pressure (0.5% and 0.8%) and high  
38 diastolic blood pressure (1.5% and 2.9%) in second and third trimesters respectively. The  
39 average weight gained by women from second to third trimester was 3.5 kg.

**Table 1: Distribution of Pregnancy non-varying Variables by preterm and term births**

| Variables                                      | Categories                                       | Total             | Term              | Preterm          |
|--|--|-------------------|-------------------|------------------|
|  |  | N=31,851<br>N (%) | N=27,059<br>N (%) | N=4,792<br>N (%) |
| Maternal Age at LMP                            | 18 to 35   | 26,206 (82.3)     | 22,423 (82.9)     | 3,783 (78.9)     |
|  | Less than 18                                     | 4,946 (15.5)      | 4,100 (15.2)      | 846 (17.7)       |
|  | More than 35                                     | 699 (2.2)         | 536 (2.0)         | 163 (3.4)        |
| Caste/Religion                                 | Brahmin and Chhetri                              | 963 (3.0)         | 857 (3.2)         | 106 (2.2)        |
|  | Vaishya  | 22,946 (72.0)     | 19,701 (72.8)     | 3,245 (67.7)     |
|  | Shudra   | 4,922 (15.5)      | 4,111 (15.2)      | 811 (16.9)       |
|  | Muslim and others                                | 2,989 (9.4)       | 2,365 (8.7)       | 624 (13.0)       |
|  | Missing  | 31 (0.1)          | 25 (0.1)          | 6 (0.1)          |
| Maternal Education                             | No schooling                                     | 21,427 (67.3)     | 17,915 (66.2)     | 3,512 (73.3)     |
|  | 1 to 5 years                                     | 2,713 (8.5)       | 2,330 (8.6)       | 383 (8.0)        |
|  | More than 5 years                                | 7,681 (24.1)      | 6,786 (25.1)      | 895 (18.7)       |
|  | Missing  | 30 (0.1)          | 28 (0.1)          | 2 (0.0)          |
| Quintiles of Wealth                            | Poorest  | 6,510 (20.4)      | 5,340 (19.7)      | 1,170 (24.4)     |
|  | Poor   | 6,380 (20.0)      | 5,403 (20.0)      | 977 (20.4)       |
|  | Middle   | 6,320 (19.8)      | 5,314 (19.6)      | 1,006 (21.0)     |
|  | Richer   | 6,296 (19.8)      | 5,470 (20.2)      | 826 (17.2)       |
|  | Richest  | 6,324 (19.9)      | 5,516 (20.4)      | 808 (16.9)       |
|  | Missing  | 21 (0.1)          | 16 (0.1)          | 5 (0.1)          |
| Maternal Height (cms)                          | <145   | 4,689 (14.7)      | 3,885 (14.4)      | 800 (16.7)       |
|  | 145-<150   | 9,559 (29.9)      | 8,025 (29.7)      | 1,527 (31.9)     |
|  | >=150  | 17,581 (55.1)     | 15,111 (55.8)     | 2,454 (51.2)     |
|  | Missing  | 51 (0.2)          | 38 (0.14)         | 11 (0.2)         |
| Parity including both LB and SB, at Enrollment | Parity 1 to 4                                    | 20,317 (63.8)     | 17,366 (64.2)     | 2,951 (61.6)     |
|  | More than 4                                      | 1,383 (4.3)       | 1,117 (4.1)       | 266 (5.6)        |
|  | Prior Pregnant but parity 0                      | 787 (2.5)         | 672 (2.5)         | 115 (2.4)        |
|  | No Prior Pregnant                                | 9,195 (28.9)      | 7,769 (28.7)      | 1,426 (29.8)     |
|  | Missing  | 169 (0.5)         | 135 (0.5)         | 34 (0.7)         |
|  | Interpregnancy Interval based on maternal recall | 18 to 36 months   | 7,927 (24.9)      | 6,787 (25.1)     |
| Any deaths among Prior LB                      | Less than 18 months                              | 11,461 (36.0)     | 9,701 (35.9)      | 1,760 (36.7)     |
|  | More than 36 months                              | 3,256 (10.2)      | 2,794 (10.3)      | 462 (9.6)        |
|  | No Prior Pregnancy                               | 9,195 (28.9)      | 7,769 (28.7)      | 1,426 (29.8)     |
|  | Missing  | 12 (0.0)          | 8 (0.0)           | 4 (0.1)          |
|  | Prior LB but not died                            | 17,488 (54.9)     | 14,999 (55.4)     | 2,489 (51.9)     |
| Any prior pregnancy ended in SB                | Prior LB died                                    | 3,618 (11.4)      | 2,999 (11.1)      | 619 (12.9)       |
|  | Prior Pregnancy but no LB                        | 1,073 (3.4)       | 909 (3.4)         | 164 (3.4)        |
|  | No prior pregnancy                               | 9,195 (28.9)      | 7,769 (28.7)      | 1,426 (29.8)     |
|  | Missing  | 477 (1.5)         | 383 (1.4)         | 94 (2.0)         |
|  | Prior Pregnancy but no SB                        | 21,270 (66.8)     | 18,127 (67.0)     | 3,143 (65.6)     |
| Any prior pregnancy ended in SB                | Prior SB   | 1,371 (4.3)       | 1,150 (4.2)       | 221 (4.6)        |
|  | No prior pregnancy                               | 9,195 (28.9)      | 7,769 (28.7)      | 1,426 (29.8)     |
|  | Missing  | 15 (0.0)          | 13 (0.0)          | 2 (0.0)          |

| Variables                                   | Categories                         | Total         | Term          | Preterm      |
|---|------------------------------------|---------------|---------------|--------------|
|   |                                    | N=31,851      | N=27,059      | N=4,792      |
|   |                                    | N (%)         | N (%)         | N (%)        |
| Any prior pregnancy ended in miscarriage    | Prior Pregnancy but no miscarriage | 19,025 (59.7) | 16,176 (59.8) | 2,849 (59.5) |
|   | Prior miscarriage                  | 3,621 (11.4)  | 3,104 (11.5)  | 517 (10.8)   |
|   | No prior pregnancy                 | 9,195 (28.9)  | 7,769 (28.7)  | 1,426 (29.8) |
|   | Missing                            | 10 (0.0)      | 10 (0.0)      | 0 (0.0)      |
| Any prior pregnancy ended in multiples      | Prior Pregnancy but no multiples   | 22,343 (70.1) | 19,030 (70.3) | 3,313 (69.1) |
|   | Prior multiples                    | 292 (0.9)     | 241 (0.9)     | 51 (1.1)     |
|   | No prior pregnancy                 | 9,195 (28.9)  | 7,769 (28.7)  | 1,426 (29.8) |
|   | Missing                            | 21 (0.1)      | 19 (0.1)      | 2 (0.0)      |
| Number of ANC visits                        | No visit                           | 5,520 (17.3)  | 4,524 (16.7)  | 996 (20.8)   |
|   | 1 visit                            | 4,146 (13.0)  | 3,420 (12.6)  | 726 (15.2)   |
|   | 2-3 visit                          | 9,779 (30.7)  | 8,158 (30.1)  | 1,621 (33.8) |
|   | 4 or more                          | 8,909 (28.0)  | 8,021 (29.6)  | 888 (18.5)   |
|   | Missing                            | 3,497 (11.0)  | 2,936 (10.9)  | 561 (11.7)   |
| Place of Delivery                           | Home/Maiti                         | 15,776 (49.5) | 13,270 (49.0) | 2,506 (52.3) |
|   | HP/Clinic/Hospital                 | 12,016 (37.7) | 10,406 (38.5) | 1,610 (33.6) |
|   | Way to Facility/Outdoors           | 610 (1.9)     | 486 (1.8)     | 124 (2.6)    |
|   | Missing                            | 3,449 (10.8)  | 2,897 (10.7)  | 552 (11.5)   |
| Bidi or tobacco use in pregnancy            | No                                 | 31,498 (98.9) | 26,789 (99.0) | 4,709 (98.3) |
|   | Yes                                | 353 (1.1)     | 270 (1.0)     | 83 (1.7)     |
| Alcohol use (jaard or rakshi) in pregnancy? | No                                 | 31,756 (99.7) | 26,982 (99.7) | 4,774 (99.6) |
|   | Yes                                | 95 (0.3)      | 77 (0.3)      | 18 (0.4)     |
| Multiple Birth                              | Singleton                          | 31,587 (99.2) | 26,946 (99.6) | 4,641 (96.8) |
|   | Twin/Triplet                       | 264 (0.8)     | 113 (0.4)     | 151 (3.2)    |
| Sex of the child                            | Female                             | 15,182 (47.7) | 13,063 (48.3) | 2,119 (44.2) |
|   | Male                               | 16,306 (51.2) | 13,794 (51.0) | 2,512 (52.4) |
|   | Twin/Triplet                       | 264 (0.8)     | 113 (0.4)     | 151 (3.2)    |
|   | Missing                            | 99 (0.3)      | 89 (0.3)      | 10 (0.2)     |
| Induction or CS done                        | Only Induction                     | 193 (0.6)     | 166 (0.6)     | 27 (0.6)     |
|   | Only CS                            | 868 (2.7)     | 735 (2.8)     | 133 (2.8)    |
|   | Both Induction and CS              | 32 (0.1)      | 28 (0.1)      | 4 (0.08)     |
|   | None                               | 30,758 (96.6) | 26130 (96.6)  | 4628 (96.6)  |

**Table 2: Distribution of pregnancy-varying variables by preterm and term births**

| Variables  |         | Total<br>N=31,851<br>N (%) | Term<br>N=27,059<br>N (%) | Preterm<br>N=4,792<br>N (%) |
|--|---------|----------------------------|---------------------------|-----------------------------|
| STI in at least one visit of 2nd trimester?                              | No      | 20,823 (65.4)              | 17,497 (64.7)             | 3,326 (69.4)                |
|  | Yes     | 4,593 (14.4)               | 3,855 (14.2)              | 738 (15.4)                  |
|  | Missing | 6,435 (20.2)               | 5,707 (21.1)              | 728 (15.2)                  |
| STI in at least one visit of 3rd trimester?                              | No      | 25,931 (81.4)              | 22,512 (83.2)             | 3,419 (71.3)                |
|  | Yes     | 2,963 (9.3)                | 2,569 (9.5)               | 394 (8.2)                   |
|  | Missing | 2,957 (9.3)                | 1,978 (7.3)               | 979 (20.4)                  |
| Respiratory Problems in at least one visit of 2nd trimester?             | No      | 17,963 (56.4)              | 15,081 (55.7)             | 2,882 (60.1)                |
|  | Yes     | 7,452 (23.4)               | 6,271 (23.2)              | 1,181 (24.6)                |
|  | Missing | 6,436 (20.2)               | 5,707 (21.1)              | 729 (15.2)                  |
| Respiratory Problems in at least one visit of 3rd trimester?             | No      | 22,860 (71.8)              | 19,743 (73.0)             | 3,117 (65.0)                |
|  | Yes     | 6,034 (18.9)               | 5,338 (19.7)              | 696 (14.5)                  |
|  | Missing | 2,957 (9.3)                | 1,978 (7.3)               | 979 (20.4)                  |
| GI Problems in at least one visit of 2nd trimester?                      | No      | 22,742 (71.4)              | 19,136 (70.7)             | 3,606 (75.3)                |
|  | Yes     | 2,673 (8.4)                | 2,216 (8.2)               | 457 (9.5)                   |
|  | Missing | 6,436 (20.2)               | 5,707 (21.1)              | 729 (15.2)                  |
| GI Problems in at least one visit of 3rd trimester?                      | No      | 26,152 (82.1)              | 22,712 (83.9)             | 3,440 (71.8)                |
|  | Yes     | 2,742 (8.6)                | 2,369 (8.8)               | 373 (7.8)                   |
|  | Missing | 2,957 (9.3)                | 1,978 (7.3)               | 979 (20.4)                  |
| Poor appetite, nausea & vomiting in at least one visit of 2nd trimester? | No      | 13,121 (41.2)              | 10,814 (40.0)             | 2,307 (48.1)                |
|  | Yes     | 12,295 (38.6)              | 10,538 (38.9)             | 1,757 (36.7)                |
|  | Missing | 6,435 (20.2)               | 5,707 (21.1)              | 728 (15.2)                  |
| Poor appetite, nausea & vomiting in at least one visit of 3rd trimester? | No      | 22,486 (70.6)              | 19,437 (71.8)             | 3,049 (63.6)                |
|  | Yes     | 6,409 (20.1)               | 5,645 (20.9)              | 764 (15.9)                  |
|  | Missing | 2,956 (9.3)                | 1,977 (7.3)               | 979 (20.4)                  |
| Vaginal Bleeding in at least one visit of 2nd trimester?                 | No      | 25,042 (78.6)              | 21,036 (77.7)             | 4,006 (83.6)                |
|  | Yes     | 373 (1.2)                  | 315 (1.2)                 | 58 (1.2)                    |
|  | Missing | 6,436 (20.2)               | 5,708 (21.1)              | 728 (15.2)                  |
| Vaginal Bleeding in at least one visit of 3rd trimester?                 | No      | 28,716 (90.2)              | 24,938 (92.2)             | 3,778 (78.8)                |
|  | Yes     | 178 (0.6)                  | 143 (0.5)                 | 35 (0.7)                    |
|  | Missing | 2,957 (9.3)                | 1,978 (7.3)               | 979 (20.4)                  |
| Swelling in at least one visit of 2nd trimester?                         | No      | 24,846 (78.0)              | 20,904 (77.3)             | 3,942 (82.3)                |
|  | Yes     | 571 (1.8)                  | 448 (1.7)                 | 123 (2.6)                   |
|  | Missing | 6,434 (20.2)               | 5,707 (21.1)              | 727 (15.2)                  |

| <b>Variables</b>  |                     | <b>Total</b>    | <b>Term</b>     | <b>Preterm</b> |
|---|---------------------|-----------------|-----------------|----------------|
|   |                     | <b>N=31,851</b> | <b>N=27,059</b> | <b>N=4,792</b> |
|   |                     | <b>N (%)</b>    | <b>N (%)</b>    | <b>N (%)</b>   |
| Swelling in at least one visit of 3rd trimester?  | No                  | 27,754 (87.1)   | 24,126 (89.2)   | 3,628 (75.7)   |
|   | Yes                 | 1,141 (3.6)     | 956 (3.5)       | 185 (3.9)      |
|   | Missing             | 2,956 (9.3)     | 1,977 (7.3)     | 979 (20.4)     |
| High Systolic BP in 2nd trimester?  | Normal Systolic BP  | 25,260 (79.3)   | 21,217 (78.4)   | 4,043 (84.4)   |
|   | High Systolic BP    | 158 (0.5)       | 136 (0.5)       | 22 (0.5)       |
|   | Missing             | 6,433 (20.2)    | 5,706 (21.1)    | 727 (15.2)     |
| High Systolic BP in 3rd trimester?  | Normal Systolic BP  | 28,659 (90.0)   | 24,905 (92.0)   | 3,754 (78.3)   |
|   | High Systolic BP    | 241 (0.8)       | 181 (0.7)       | 60 (1.3)       |
|   | Missing             | 2,951 (9.3)     | 1,973 (7.3)     | 978 (20.4)     |
| High diastolic BP in 2nd trimester?   | Normal diastolic BP | 24,945 (78.3)   | 20,976 (77.5)   | 3,969 (82.8)   |
|   | High diastolic BP   | 473 (1.5)       | 377 (1.4)       | 96 (2.0)       |
|   | Missing             | 6,433 (20.2)    | 5,706 (21.1)    | 727 (15.2)     |
| High diastolic BP in 3rd trimester?   | Normal diastolic BP | 27,982 (87.9)   | 24,360 (90.0)   | 3,622 (75.6)   |
|   | High diastolic BP   | 918 (2.9)       | 726 (2.7)       | 192 (4.0)      |
|   | Missing             | 2,951 (9.3)     | 1,973 (7.3)     | 978 (20.4)     |
| Average weight in 3rd trimester minus Average weight in 2nd trimester in kg (Mean (SD)) |                     | 3.5 (2.1)       | 3.6 (2.1)       | 2.9 (2.2)      |

## Outcome data

There were 4,792 preterm births out of 31,851 pregnancies with at least one LB. Hence, the prevalence of preterm birth was 15% (95% CI: 14.6%, 15.4%) among the pregnancies enrolled between September 9, 2010, to January 16, 2017. Spontaneous preterm birth was 14.5% and non-spontaneous preterm birth was 0.5%. On looking at severity of spontaneous preterm birth, the prevalence were 0.5%, 1.4% and 2.1% and 10.5% for extreme PTB (<28 weeks), very PTB (28-<32 weeks), moderate PTB (32-<34 weeks) and late PTB (34-<37 weeks) respectively.

## Main results

The main results are shown in Table 3. Pregnancy non-varying variables that increased the risk of spontaneous preterm were maternal age less than 18 (ARR=1.13, 95% CI: 1.02-1.26); being Muslim compared to Brahmin and Chhetri (1.53, 1.16-2.01); first pregnancy as compared to parity 1 to 4 (1.15, 1.04-1.28); having a multiple birth (4.91, 4.20-5.75) and having a male child (1.10, 1.02-1.17). Pregnancy non-varying variables that decreased the risk of spontaneous preterm were maternal education of more than 5 years (0.81, 0.73-0.90); maternal height of  $\geq 150$  cm (0.89, 0.81-0.98) and being wealthier: richer (0.83, 0.74-0.93) wealth quintile compared to the poorest wealth quintile. Pregnancy non-varying variables that showed no association with spontaneous preterm births in the bivariable/unadjusted models are any prior pregnancy ending in SB, any prior pregnancy ending in multiples, and any prior pregnancy ending in miscarriage, and interpregnancy interval. The pregnancy non-varying variable that showed an association in the bivariable model, but not in the multivariable models was any prior pregnancy ending in death for a live birth.

For morbidity symptoms, some increased the risk of preterm, and all of these showed increased risk when symptoms were present in the 3<sup>rd</sup> trimester. Having vaginal bleeding (ARR= 1.53, 95% CI: 1.08-2.18); swelling (1.37, 1.17-1.60); high systolic BP (1.47, 1.08-2.01) and high diastolic BP (1.41, 1.17-1.70) in the 3<sup>rd</sup> trimester significantly increased the risk of spontaneous preterm. Some symptom variables significantly decreased the risk of spontaneous preterm. Having respiratory problem in the 3<sup>rd</sup> trimester (0.86, 0.79-0.94); and having poor appetite, nausea and vomiting in the 2<sup>nd</sup> trimester (0.86, 0.80-0.92) and in the 3<sup>rd</sup> trimester (0.86, 0.79-0.94) decreased the risk of spontaneous preterm. Symptom variables that showed no association with spontaneous preterm were STI and GI problems. Symptom variables that were



significant in the bivariable model, but not significant in the multivariable models were swelling in the 2<sup>nd</sup> trimester and diastolic blood pressure in the 2<sup>nd</sup> trimester. For maternal weight, higher weight gain from the 2<sup>nd</sup> to the 3<sup>rd</sup> trimester was associated with a decreased the risk of spontaneous preterm (0.89, 0.87-0.90).

To examine the possible bias associated with exclusion of pregnancies with missing data, we compared characteristics of women excluded in the regression analysis (n=9,461) (mainly because of missing morbidity in 2<sup>nd</sup> trimester due to late enrollment) with those included in the regression analysis (n=21,297) (supplementary Table S1). The women excluded in the regression analysis were slightly better off than those included in the regression based on education and socioeconomic status but most relevant, the spontaneous preterm prevalence was 17.9% for those excluded in the regression compared to 13.8% included in the regression.

We also reran the regression model including number of ANC visits. The fewer the number of ANC visits, the higher the risk of spontaneous preterm birth (Table S2). The other regression coefficients did not change in any qualitative way. This could be due to fewer ANC visits putting women at higher risk for spontaneous preterm birth as services provided in ANC (counseling, iron folic acid tablets, blood pressure and weight measurements) are provided less often, but this association may also be due to a shorter duration of pregnancy leading to less time available for ANC visits.

**Table 3: Crude and Adjusted Risk Ratios for associations between risk factors and spontaneous preterm birth**

| Name of Variables           | Categories          | Unadjusted Model<br>Risk Ratio (95% CI) | Adjusted Model<br>(N=21,297)<br>Risk Ratio (95% CI) |
|-----------------------------|---------------------|---|---|
| Maternal Age at LMP         | 18 to 35            | 1                                       | 1   |
|                             | Less than 18        | 1.19*** [1.11,1.28]                     | 1.13* [1.02,1.26]                                   |
|                             | More than 35        | 1.57*** [1.36,1.81]                     | 1.22 [0.98,1.51]                                    |
| Caste/Religion Categories   | Brahmin and Chhetri | 1                                       | 1   |
|                             | Vaishya             | 1.33** [1.09,1.62]                      | 1.23 [0.95,1.59]                                    |
|                             | Shudra              | 1.55*** [1.26,1.90]                     | 1.23 [0.94,1.62]                                    |
|                             | Muslim and others   | 1.96*** [1.60,2.42]                     | 1.53** [1.16,2.01]                                  |
| Mother's Years of Education | No schooling        | 1                                       | 1   |
|                             | 1 to 5 years        | 0.86** [0.78,0.95]                      | 0.91 [0.80,1.03]                                    |
|                             | More than 5 years   | 0.71*** [0.66,0.76]                     | 0.81*** [0.73,0.90]                                 |
| Quintiles of Wealth         | Poorest             | 1                                       | 1   |
|                             | Poor                | 0.86*** [0.79,0.93]                     | 0.90* [0.82,1.00]                                   |
|                             | Middle              | 0.89** [0.82,0.96]                      | 0.95 [0.86,1.05]                                    |

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| Name of Variables  | Categories                         | Unadjusted Model<br>Risk Ratio (95% CI) | Adjusted Model<br>(N=21,297)<br>Risk Ratio (95% CI) |
|--|------------------------------------|---|---|
| Mother's height(centimeter)  | Richer                             | 0.73*** [0.67,0.79]                     | 0.83** [0.74,0.93]                                  |
|  | Richest                            | 0.71*** [0.65,0.77]                     | 0.88* [0.78,1.00]                                   |
|  | <145                               | 1                                       | 1   |
|  | 145-<150                           | 0.93 [0.86,1.01]                        | 0.98 [0.88,1.08]                                    |
| Parity including both LB and SB, at Enrollment                           | >=150                              | 0.81*** [0.75,0.87]                     | 0.89* [0.81,0.98]                                   |
|  | Parity 1 to 4                      | 1                                       | 1   |
|  | More than 4                        | 1.32*** [1.17,1.48]                     | 1.17 [0.99,1.37]                                    |
| Interpregnancy Intervals   | Prior Pregnant but parity 0        | 1.02 [0.85,1.22]                        | 0.92 [0.62,1.37]                                    |
|  | No Prior Pregnant                  | 1.10** [1.04,1.17]                      | 1.15** [1.04,1.28]                                  |
|  | 18 to 36 months                    | 1                                       | 1   |
| Any death among prior LB   | Less than 18 months                | 1.07 [0.99,1.14]                        | 1.08 [0.99,1.18]                                    |
|  | More than 36 months                | 0.98 [0.89,1.09]                        | 0.9 [0.79,1.02]                                     |
|  | No Prior Pregnancy                 | 1.11** [1.03,1.20]                      | 1 [1.00,1.00]                                       |
|  | Prior LB but not died              | 1                                       | 1   |
| Any prior pregnancy ended in SB  | Prior LB died                      | 1.19*** [1.09,1.29]                     | 1.07 [0.97,1.19]                                    |
|  | Prior Pregnancy but no LB          | 1.07 [0.92,1.25]                        | 1.06 [0.75,1.49]                                    |
|  | No prior pregnancy                 | 1.12*** [1.06,1.19]                     | 1 [1.00,1.00]                                       |
| Any prior pregnancy ended in miscarriage                                 | Prior Pregnancy but no SB          | 1                                       | 1   |
|  | Prior SB                           | 1.08 [0.94,1.23]                        | 1.08** [1.02,1.15]                                  |
|  | No Prior Pregnancy                 | 1.08** [1.02,1.15]                      | 1   |
| Any prior pregnancy ended in multiples                                   | Prior Pregnancy but no miscarriage | 1                                       | 1   |
|  | Prior miscarriage                  | 0.94 [0.86,1.03]                        | 1.07* [1.01,1.13]                                   |
|  | No Prior Pregnancy                 | 1.07* [1.01,1.13]                       | 1   |
| Multiple Birth   | Prior Pregnancy but no multiples   | 1                                       | 1   |
|  | Prior multiples                    | 1.14 [0.87,1.49]                        | 1.14 [0.87,1.49]                                    |
|  | No prior pregnancy                 | 1.08** [1.02,1.14]                      | 1.08** [1.02,1.17]                                  |
| Sex of the child   | Singleton                          | 1                                       | 1   |
|  | Twin/Triplet                       | 3.92*** [3.52,4.38]                     | 4.91*** [4.20,5.75]                                 |
|  | Female                             | 1                                       | 1   |
| STI in at least one visit of 2nd trimester?                              | Male                               | 1.10*** [1.04,1.17]                     | 1.10** [1.02,1.17]                                  |
|  | Twin/Triplet                       | 4.13*** [3.69,4.63]                     | 1   |
|  | No                                 | 1                                       | 1   |
| STI in at least one visit of 3rd trimester?                              | Yes                                | 0.99 [0.92,1.07]                        | 1   |
|  | No                                 | 1                                       | 1   |
| Respiratory Problems in at least one visit of 2nd trimester?             | Yes                                | 1.01 [0.92,1.12]                        | 1   |
|  | No                                 | 1                                       | 1   |
| Respiratory Problems in at least one visit of 3rd trimester?             | Yes                                | 1 [0.94,1.06]                           | 1.08 [1.00,1.16]                                    |
|  | No                                 | 1                                       | 1   |
| GI Problems in at least one visit of 2nd trimester?                      | Yes                                | 0.85*** [0.79,0.92]                     | 0.86** [0.79,0.94]                                  |
|  | No                                 | 1                                       | 1   |
| GI Problems in at least one visit of 3rd trimester?                      | Yes                                | 1.08 [0.98,1.18]                        | 1   |
|  | No                                 | 1                                       | 1   |
| Poor appetite, nausea & vomiting in at least one visit of 2nd trimester? | Yes                                | 1.04 [0.94,1.16]                        | 1   |
|  | No                                 | 1                                       | 1   |
| Poor appetite, nausea & vomiting in at least                             | Yes                                | 0.81*** [0.77,0.86]                     | 0.86*** [0.80,0.92]                                 |
|  | No                                 | 1                                       | 1   |

| Name of Variables   | Categories          | Unadjusted Model<br>Risk Ratio (95% CI) | Adjusted Model<br>(N=21,297)<br>Risk Ratio (95% CI) |
|---|---------------------|---|---|
| one visit of 3rd trimester?   | Yes                 | 0.88** [0.82,0.95]                      | 0.86*** [0.79,0.94]                                 |
| Vaginal Bleeding in at least one visit of 2nd trimester?                      | No                  | 1                                       | 1   |
|   | Yes                 | 0.91 [0.71,1.17]                        | 0.84 [0.71,1.17]                                    |
| Vaginal Bleeding in at least one visit of 3rd trimester?                      | No                  | 1                                       | 1   |
|   | Yes                 | 1.44* [1.05,1.98]                       | 1.53*[1.08,2.18]                                    |
| Swelling in at least one visit of 2nd trimester?                              | No                  | 1                                       | 1   |
|   | Yes                 | 1.32*** [1.12,1.55]                     | 1.19 [0.98,1.46]                                    |
| Swelling in at least one visit of 3rd trimester?                              | No                  | 1                                       | 1   |
|   | Yes                 | 1.25** [1.09,1.44]                      | 1.37*** [1.17,1.60]                                 |
| High Systolic BP in 2nd trimester?  | Normal Systolic BP  | 1                                       | 1   |
|   | High Systolic BP    | 0.89 [0.59,1.34]                        | 0.67 [0.40,1.12]                                    |
| High Systolic BP in 3rd trimester?  | Normal Systolic BP  | 1                                       | 1   |
|   | High Systolic BP    | 1.92*** [1.52,2.41]                     | 1.47* [1.08,2.01]                                   |
| High diastolic BP in 2nd trimester?   | Normal diastolic BP | 1                                       | 1   |
|   | High diastolic BP   | 1.34** [1.12,1.60]                      | 1.09 [0.85,1.40]                                    |
| High diastolic BP in 3rd trimester?   | Normal diastolic BP | 1                                       | 1   |
|   | High diastolic BP   | 1.57*** [1.37,1.80]                     | 1.41*** [1.17,1.70]                                 |
| Average weight in 3rd trimester minus<br>Average weight in 2nd trimester (kg) |                     | 0.88*** [0.87,0.90]                     | 0.89*** [0.87,0.90]                                 |

\*  $p < 0.05$ , \*\*  $p < 0.01$ , \*\*\*  $p < 0.001$

## DISCUSSION

Our study is one of the only large-scale studies on preterm births using data from an existing pregnancy surveillance in rural Sarlahi, Nepal. The prevalence of preterm birth is 15%, higher than previous estimates from Nepal [18, 19] which were primarily from urban areas and large hospital-based studies. Our study's strength is that it was population-based and included all home and facility deliveries but is confined to a rural and relatively small geographic area (one third of a district). Our study population is not necessarily representative of all of Nepal, but it is representative of Province 2 in the Terai region within which Sarlahi district is located. For example, the NMR in our study was 31 per 1000 live births. This is similar to the NMR in the 2016 Nepal Demographic Health Survey (NDHS) for Province 2 (30 per 1000). Similarly, 67% of women in our study had no schooling, slightly higher than the 61% in the NDHS for Province 2. NDHS did not provide data on ANC 4+ for Province 2 but rural areas of Nepal had 62% coverage of ANC 4+. It should be noted in our study that health care seeking in pregnancy is low considering the low rates of 4 or more ANC visits (28%) and facility deliveries (38%). The low rates of induction and caesarean section point to a very low proportion of the PTBs being due to iatrogenic causes.

In many other settings, both younger and older maternal age have been reported to be risk factors for preterm birth. [24-30] Being from Muslim caste was positively associated with preterm as compared to Brahmin/Chhetri, which constitutes the major caste in Nepal. Caste/religion is a social construction, and studies in different places have shown that women in minor caste/race/color have higher risk of preterm births. [31-33] It significantly matters what position an individual holds within a society, with regards to occurrence of diseases and also their unequal distribution.[34-36]. First pregnancy (primipara) has been shown to be associated with spontaneous preterm birth in other studies. A study in France showed that primipara as compared to parity 2-3 increased the risk of preterm birth by 1.8 times.[37] Another study in the USA showed that being primipara as compared to multipara increased the risk of very preterm and extremely preterm birth, with the highest risk of 1.37 times for extremely preterm birth.[38] Meta-analysis done using 14 cohort studies from LMICs [39] and a study from sub-saharan African countries [40] also show that primiparity is associated with increased odds of preterm birth. Primipara is a risk factor for hypertensive disorders of pregnancy (HDP), which increases the risk of preterm birth.[41] Our study did not show interpregnancy interval to be the risk factor for spontaneous preterm birth. However, other

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3 studies on relationships between interpregnancy interval and preterm birth consistently showed  
4 that shorter interpregnancy intervals increase the risk of preterm births. However, the intervals  
5 used were not uniform across studies. One study found that, compared to an IPI of 18–23  
6 months, IPIs <3, 3–5, and 6–12 months had higher risks for preterm birth.[42] Another study  
7 with median IPI of 36 months showed that, compared to an IPI of 24–36 months, an IPI of  
8 <24 months was associated with preterm delivery.[43] Different studies corroborate our  
9 finding that multiple births are a risk factor for preterm birth. [18, 44, 45] Similar to our study,  
10 others also found male children at higher risk of being preterm[46-48], but a study in Nepal  
11 found that female children had a higher risk of being preterm.[18] This study in Nepal enrolled  
12 live births in a hospital setting, and had almost half the prevalence of our study. [18] They  
13 could have missed more males that had preterm births at home or on the way to a facility.  
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24 Different studies in Nepal [18] and outside of Nepal [49-51] have also shown that higher  
25 education of mothers decreases the risk of preterm births. Higher education of mothers can lead  
26 to increased knowledge and awareness regarding pregnancy-related care and thus decrease  
27 adverse outcomes of pregnancy. We found greater maternal height to be protective for  
28 spontaneous preterm birth, similar to the findings from a meta-analysis done using 12 cohort  
29 studies from LMICs. [52] .We found that women in the richer wealth quintile had a lower risk  
30 of spontaneous preterm births. Having higher household economic status probably does not  
31 directly affect the gestational age at outcome, instead, it probably is mediated by factors like  
32 nutrition, physically demanding work during pregnancy, type of care at home, stress level and  
33 other psychological factors.[53]  
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43 Pregnancy-varying morbidities that significantly decreased the risk of preterm birth in our  
44 analysis were respiratory problems in the 3<sup>rd</sup> trimester; and poor appetite, nausea and vomiting  
45 in the 2<sup>nd</sup> trimester, and the 3<sup>rd</sup> trimester. On segregating the symptoms within respiratory  
46 problems , we found that it was the persistent cough in the 3<sup>rd</sup> trimester that decreased the risk  
47 of preterm. A similar relationship was found between persistent cough and Large for  
48 Gestational Age (LGA) in another study done using the same data as ours. [54] However, we  
49 could not find any such association in the previous literature. The association might be due to  
50 some unmeasured confounders. Or it could be that women with persistent cough in the  
51 3<sup>rd</sup> trimester made more frequent check-up visits. We saw that 40% of women with persistent  
52 cough in the 3<sup>rd</sup> trimester sought treatment for cough, and almost all had sought treatment  
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3 more than once. The pathogenesis of nausea and vomiting in pregnancy is not very clear, but  
4 it is broadly accepted to be multifactorial, with the involvement of genetic, endocrine, and  
5 gastrointestinal factors. [55] Our findings corroborate with previous findings that nausea and  
6 vomiting is associated with reduced risk of preterm birth. [56-59] Specifying by trimesters, a  
7 study by Wallin et. al. in Nepal showed similar findings - poor appetite, nausea and vomiting  
8 in first trimester was not significantly associated with spontaneous preterm births, but having  
9 these symptoms in the 2<sup>nd</sup> trimester decreased the risk of spontaneous preterm by 25%. [60]  
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17 Pregnancy-varying morbidities that significantly increased the risk of spontaneous preterm  
18 birth were vaginal bleeding, swelling of hands and face, high diastolic and systolic BP, all in  
19 the 3<sup>rd</sup> trimester. Other studies show similar results for vaginal bleeding. Vaginal bleeding is  
20 associated with fetal exposure to oral pathogens, which thereby increases the risk of  
21 spontaneous preterm birth, however, whether bleeding is the cause or result of fetal exposure  
22 to oral pathogens is not clear. [61] A prospective cohort study, separating first and second  
23 trimesters showed that vaginal bleeding in both trimesters increased the risk of preterm birth  
24 by 3.6 times, while bleeding in the second trimester only, was not associated with preterm  
25 birth. [62] A systematic review using 23 studies showed that bleeding in early pregnancy  
26 increased the risk of preterm births. [63] A study in China showed that vaginal bleeding in the  
27 first-trimester increased the risk of preterm births, and the severity, duration and initial timing  
28 of vaginal bleeding had different effects on the severity of preterm births. [61] Due to the low  
29 enrollment of women in the 1<sup>st</sup> trimester, we could not look at the association of vaginal  
30 bleeding in the 1<sup>st</sup> trimester with spontaneous preterm birth. However, all of the above  
31 information indicates that vaginal bleeding can be an important predictor of spontaneous  
32 preterm birth and health care workers should recommend appropriate interventions for women  
33 if they present with vaginal bleeding (such as more frequent follow up or referral for higher  
34 level care).  
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50 Other studies on blood pressure during pregnancy have also shown that a rise in systolic BP  
51 (over 30 mm Hg) or diastolic BP (over 15mm Hg), from early pregnancy to the mid third  
52 trimester significantly increased the risk of spontaneous preterm birth by 2 to 3 times. [64]  
53 Another study showed that an increase in 10 mm Hg in diastolic BP increased the risk of  
54 preterm birth by 29%. [65] These indicate the importance of measuring BP during the 3<sup>rd</sup>  
55 trimester. High BP in the 3<sup>rd</sup> trimester is an indicator of pre-eclampsia/eclampsia and can  
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3 predict preterm birth. Measuring BP frequently and monitoring the rise and cause of increased  
4 BP is important for predicting spontaneous preterm birth.  
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8 For maternal weight, higher weight gain from the 2nd to the 3rd trimester decreased the risk of  
9 spontaneous preterm birth. This is consistent with a study done outside Nepal, which showed  
10 that very low weight gain was strongly associated with very preterm delivery, and that this  
11 varied by pre-pregnancy BMI, where underweight women had the highest association and very  
12 obese women had lowest association with preterm.[66] Our study was conducted in a non-  
13 obese and undernourished population. We do not have pre-pregnancy BMI, so we looked at  
14 the mean BMI in the first trimester. Though the first trimester represents less than half of the  
15 pregnancies in the study, it hints at undernutrition in the population. The mean BMI was 19.1  
16 kg/m<sup>2</sup>, and 37% had BMI less than 18.5 kg/m<sup>2</sup>. So, less maternal weight gain in such  
17 population can pose a risk to spontaneous preterm births. Given spontaneous preterm births  
18 have shorter gestation, the increase in weight gain will likely be less because there is less time  
19 to increase weight, especially in the third trimester, when much of the gestational weight is  
20 gained.  
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### 34 **Strengths and Limitations**

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36 This was a large population-based study that was generally representative of the rural Terai  
37 region of Nepal. Multiple variables were collected, including socioeconomic, demographic,  
38 pregnancy history, and monthly morbidity in pregnancy that could be examined as risk factors  
39 for spontaneous preterm birth. Although there was some missing data in regression analyses, a  
40 comparison of those with and without missing data did not show large differences in risk factor  
41 prevalence. However, those missing data had higher prevalence of preterm birth. It is possible  
42 that if women with missing data were included in the regression, we may have seen stronger  
43 associations but the potential bias of these differences is unclear. Gestational age (GA) at birth  
44 was measured using date of last menstrual period (LMP) as usually done in the LMICs rather  
45 than by ultrasound. However, as LMP was asked at enrollment which was generally early in  
46 pregnancy, there is less recall bias than LMP recalled at delivery or late in pregnancy. Using  
47 the same method as we used to obtain LMP, Gernand et al. found that LMP based estimates of  
48 GA in rural Bangladesh were a mean 2.8 days longer than what was obtained on ultrasound.  
49 [67] We therefore believe that this is probably not a significant limitation. Women were  
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3 followed prospectively at monthly intervals to reduce recall bias about pregnancy morbidities  
4 and symptoms. In order to reduce misclassification of stillbirths and live births, women were  
5 asked whether the infant moved, breathed or cried after birth.  
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10 Some variables associated with increased risk of spontaneous preterm births in previous  
11 studies, for example, a prior pregnancy ending in a preterm birth, gestational diabetes, maternal  
12 anemia and pre-pregnancy maternal nutritional status were not measured in the main trial.  
13 However, other important morbidity variables were measured and used in the analysis. Some  
14 covariates were highly correlated with each other (such as some reproductive history ones) and  
15 so, not all were included in the multivariable regression. Some covariates were not statistically  
16 significant in unadjusted analyses and there was not a compelling biological or sociological  
17 reason to include them in the adjusted model. Other important variables like smoking and  
18 alcohol, although measured, could not be included in the final regression analysis as their  
19 prevalence was very low in this population. We believe these risk factors are likely  
20 generalizable for similar populations in South Asia.  
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## 31 **CONCLUSION**

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34 Preterm birth is a leading risk factor for neonatal and under-5 mortality and morbidity  
35 worldwide. To reduce neonatal mortality, preventing preterm births can be a vital step. Some  
36 of the risk factors from our study are amenable to antenatal interventions but many others need  
37 more understanding of the underlying causal mechanisms. Maternal education and awareness  
38 can play a role in the long term, while good quality antenatal care, as suggested by the new  
39 WHO recommendation of 8 contacts during pregnancy, may help reduce some PTBs. Future  
40 research should focus on basic research involving the field of ‘omics’ using biological samples  
41 and implementation research to improve antenatal care and maternal nutrition.  
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## 49 **OTHER INFORMATION**

### 50 **Authors' contribution:**

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52 SS, EH, DM, SZ, REB and JK conceptualized and designed the analysis. SS conducted the  
53 analysis and wrote the manuscript. LCM, JMT, SKK, SLC and JK were investigators in the  
54 parent trial. All authors reviewed results, analysis, discussed interpretations, and contributed  
55 to development and revision of the manuscript.  
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**Competing interests:**

The authors declare that they have no competing interests.

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**Availability of data and materials:**

No data are available.

**Consent for publication:**

No individual information including data, images and video are included in this manuscript.

**Ethics approval and consent to participate:**

NOMS was approved by the institutional review board (IRB) of the Johns Hopkins Bloomberg School of Public Health in the USA and by the IRB of the Institute of Medicine, Tribhuvan University, Kathmandu, Nepal. This analysis of secondary data was considered exempt by the Johns Hopkins Bloomberg School of Public Health institutional review board (IRB) (FWA00000287). Verbal consent was obtained from women for their participation and their infants for the primary data collection.

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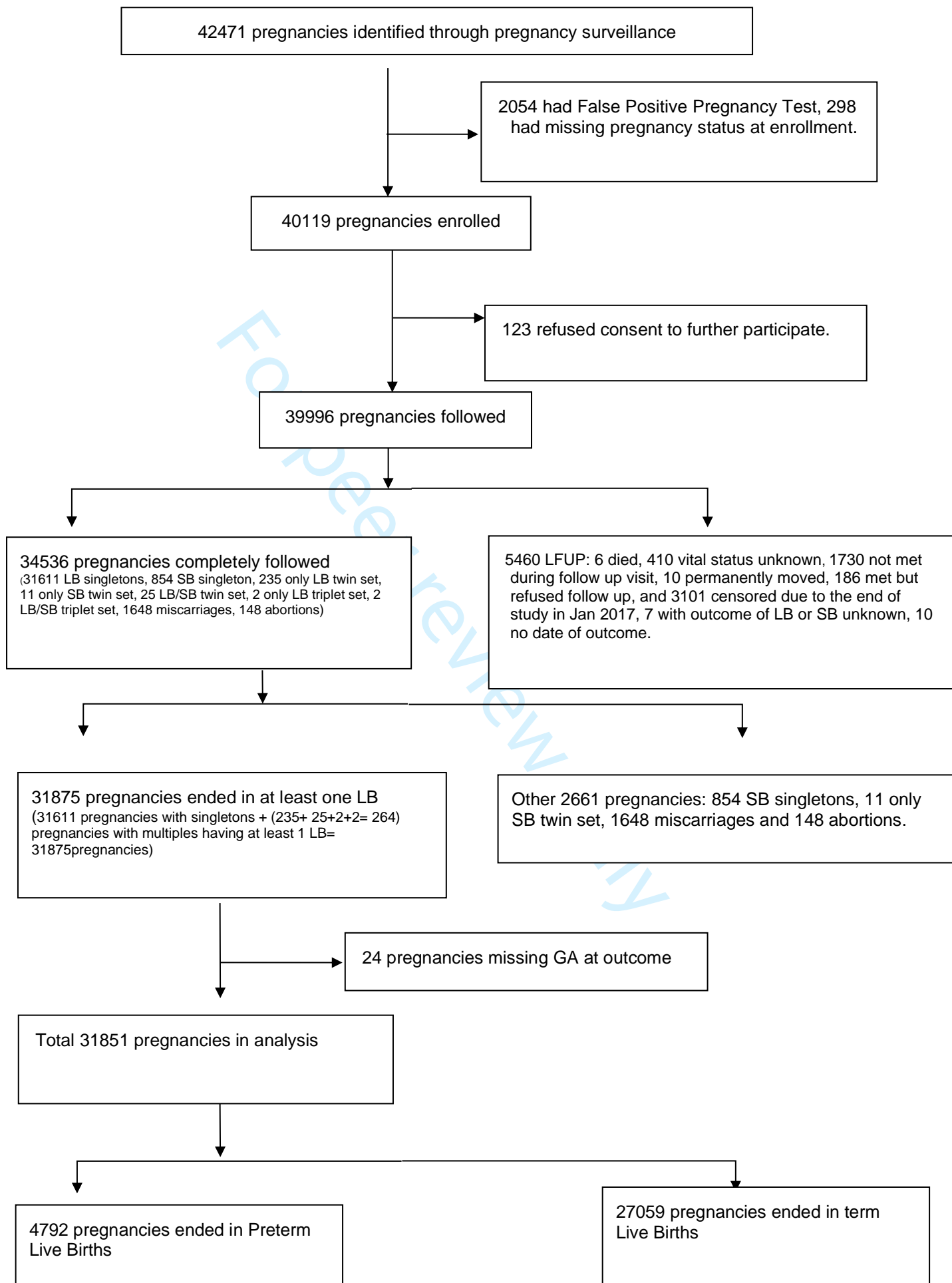
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29 Figure 1- Flow Diagram of Participants  
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**Figure 1: Flow Diagram for Participants**



## SUPPLEMENTARY TABLES

Table S1. Comparing Pregnancy non-varying Variables by pregnancies Included and Excluded in the Regression Analysis

| Variables  | Categories                  | Total             | Included in regression | Excluded in regression | p-value |
|--|-----------------------------|-------------------|------------------------|------------------------|---------|
|  |                             | N=30,758<br>N (%) | N=21,297<br>N (%)      | N=9,461<br>N (%)       |         |
| Maternal Age at LMP                              | 18 to 35                    | 25,300 (82.3)     | 17,683 (83.0)          | 7,617 (80.5)           | <0.001  |
|  | Less than 18                | 4,792 (15.6)      | 3,169 (14.9)           | 1,623 (17.2)           |         |
|  | More than 35                | 666 ( 2.2)        | 445 ( 2.1)             | 221 ( 2.3)             |         |
| Caste/Ethnicity Categories                       | Brahmin and Chhetri         | 879 ( 2.9)        | 661 ( 3.1)             | 218 ( 2.3)             | <0.001  |
|  | Vaishya                     | 22,104 (71.9)     | 15,412 (72.4)          | 6,692 (70.7)           |         |
|  | Shudra                      | 4,826 (15.7)      | 3,392 (15.9)           | 1,434 (15.2)           |         |
|  | Muslim and others           | 2,919 ( 9.5)      | 1,832 ( 8.6)           | 1,087 (11.5)           |         |
|  | Missing                     | 30 ( 0.1)         | 0 ( 0.0)               | 30 ( 0.3)              |         |
| Mother's Education                               | No schooling                | 20,891 (67.9)     | 14,561 (68.4)          | 6,330 (66.9)           | 0.032   |
|  | 1 to 5 years                | 2,613 ( 8.5)      | 1,819 ( 8.5)           | 794 ( 8.4)             |         |
|  | More than 5 years           | 7,224 (23.5)      | 4,917 (23.1)           | 2,307 (24.4)           |         |
|  | Missing                     | 30 ( 0.1)         | 0 ( 0.0)               | 30 ( 0.3)              |         |
| Quintiles of Wealth                              | Poorest                     | 6,354 (20.7)      | 4,414 (20.7)           | 1,940 (20.5)           | 0.004   |
|  | Poorer                      | 6,210 (20.2)      | 4,386 (20.6)           | 1,824 (19.3)           |         |
|  | Middle                      | 6,152 (20.0)      | 4,289 (20.1)           | 1,863 (19.7)           |         |
|  | Richer                      | 6,036 (19.6)      | 4,172 (19.6)           | 1,864 (19.7)           |         |
|  | Richest                     | 5,985 (19.5)      | 4,036 (19.0)           | 1,949 (20.6)           |         |
|  | Missing                     | 21 ( 0.1)         | 0 ( 0.0)               | 21 ( 0.2)              |         |
| Maternal Height (centimeter)                     | <145                        | 4,510 (14.7)      | 3,193 (15.0)           | 1,317 (13.9)           | 0.042   |
|  | 145-<150                    | 9,227 (30.0)      | 6,413 (30.1)           | 2,814 (29.7)           |         |
|  | >=150                       | 16,974 (55.2)     | 11,691 (54.9)          | 5,283 (55.8)           |         |
|  | Missing                     | 47 ( 0.2)         | 0 ( 0.0)               | 47 ( 0.5)              |         |
| Parity including both LB and SB, at Enrollment   | Parity 1 to 4               | 19,805 (64.4)     | 14,137 (66.4)          | 5,668 (59.9)           | <0.001  |
|  | More than 4                 | 1,351 ( 4.4)      | 875 ( 4.1)             | 476 ( 5.0)             |         |
|  | Prior Pregnant but parity 0 | 723 ( 2.4)        | 515 ( 2.4)             | 208 ( 2.2)             |         |
|  | No Prior Pregnant           | 8,717 (28.3)      | 5,770 (27.1)           | 2,947 (31.1)           |         |
|  | Missing                     | 162 ( 0.5)        | 0 ( 0.0)               | 162 ( 1.7)             |         |
| Interpregnancy Interval based on maternal recall | 18 to 36 months             | 7,723 (25.1)      | 5,540 (26.0)           | 2,183 (23.1)           | <0.001  |
|  | Less than 18 months         | 11,201 (36.4)     | 7,693 (36.1)           | 3,508 (37.1)           |         |
|  | More than 36 months         | 3,106 (10.1)      | 2,294 (10.8)           | 812 ( 8.6)             |         |
|  | No Prior Pregnancy          | 8,717 (28.3)      | 5,770 (27.1)           | 2,947 (31.1)           |         |
|  | Missing                     | 11 ( 0.0)         | 0 ( 0.0)               | 11 ( 0.1)              |         |
| Any deaths among Prior LB                        | Prior LB but not died       | 17,089 (55.6)     | 12,273 (57.6)          | 4,816 (50.9)           | <0.001  |
|  | Prior LB died               | 3,518 (11.4)      | 2,555 (12.0)           | 963 (10.2)             |         |
|  | Prior Pregnancy but no LB   | 980 ( 3.2)        | 699 ( 3.3)             | 281 ( 3.0)             |         |
|  | No prior pregnancy          | 8,717 (28.3)      | 5,770 (27.1)           | 2,947 (31.1)           |         |
|  | Missing                     | 454 ( 1.5)        | 0 ( 0.0)               | 454 ( 4.8)             |         |
| Any prior pregnancy ended in SB                  | Prior pregnancy but no SB   | 20,736 (67.4)     | 14,704 (69.0)          | 6,032 (63.8)           | <0.001  |

| Variables                                       | Categories                         | Total           | Included in regression | Excluded in regression | p-value |
|---|------------------------------------|-----------------|------------------------|------------------------|---------|
|   |                                    | <b>N=30,758</b> | <b>N=21,297</b>        | <b>N=9,461</b>         |         |
|   | Prior SB                           | 1,291 ( 4.2)    | 815 ( 3.8)             | 476 ( 5.0)             |         |
|   | No prior pregnancy                 | 8,717 (28.3)    | 5,770 (27.1)           | 2,947 (31.1)           |         |
|   | Missing                            | 14 ( 0.0)       | 8 ( 0.0)               | 6 ( 0.1)               |         |
| Any prior pregnancy ended in miscarriage?       | Prior pregnancy but no miscarriage | 18,554 (60.3)   | 12,959 (60.8)          | 5,595 (59.1)           | <0.001  |
|   | Prior miscarriage                  | 3,478 (11.3)    | 2,565 (12.0)           | 913 ( 9.7)             |         |
|   | No prior pregnancy                 | 8,717 (28.3)    | 5,770 (27.1)           | 2,947 (31.1)           |         |
|   | Missing                            | 9 ( 0.0)        | 3 ( 0.0)               | 6 ( 0.1)               |         |
| Any prior pregnancy ended in multiples?         | Prior pregnancy but no multiples   | 21,735 (70.7)   | 15,383 (72.2)          | 6,352 (67.1)           | <0.001  |
|   | Prior multiples                    | 286 ( 0.9)      | 135 ( 0.6)             | 151 ( 1.6)             |         |
|   | No prior pregnancy                 | 8,717 (28.3)    | 5,770 (27.1)           | 2,947 (31.1)           |         |
|   | Missing                            | 20 ( 0.1)       | 9 ( 0.0)               | 11 ( 0.1)              |         |
| Number of ANC visits                            | No visit                           | 5,431 (17.7)    | 3,788 (17.8)           | 1,643 (17.4)           | <0.001  |
|   | 1 visit                            | 4,047 (13.2)    | 2,836 (13.3)           | 1,211 (12.8)           |         |
|   | 2-3 visit                          | 9,443 (30.7)    | 6,809 (32.0)           | 2,634 (27.8)           |         |
|   | 4 or more                          | 8,342 (27.1)    | 6,532 (30.7)           | 1,810 (19.1)           |         |
|   | Missing                            | 3,495 (11.4)    | 1,332 ( 6.3)           | 2,163 (22.9)           |         |
| Place of Delivery                               | Home/Maiti                         | 15,669 (50.9)   | 11,348 (53.3)          | 4,321 (45.7)           | 0.002   |
|   | HP/Clinic/Hospital                 | 11,038 (35.9)   | 8,210 (38.6)           | 2,828 (29.9)           |         |
|   | Way to Facility/Outdoors           | 602 ( 2.0)      | 439 ( 2.1)             | 163 ( 1.7)             |         |
|   | Missing                            | 3,449 (11.2)    | 1,300 ( 6.1)           | 2,149 (22.7)           |         |
| Bidi or tobacco use in pregnancy                | No                                 | 30,410 (98.9)   | 21,060 (98.9)          | 9,350 (98.8)           | 0.64    |
|   | Yes                                | 348 ( 1.1)      | 237 ( 1.1)             | 111 ( 1.2)             |         |
| Alcohol use (jaard or rakshi) in pregnancy?     | No                                 | 30,665 (99.7)   | 21,230 (99.7)          | 9,435 (99.7)           | 0.56    |
|   | Yes                                | 93 ( 0.3)       | 67 ( 0.3)              | 26 ( 0.3)              |         |
| Multiple Birth                                  | Singleton                          | 30,508 (99.2)   | 21,147 (99.3)          | 9,361 (98.9)           | 0.001   |
|   | Twin/Triplet                       | 250 ( 0.8)      | 150 ( 0.7)             | 100 ( 1.1)             |         |
| Sex of the child                                | Female                             | 14,673 (47.7)   | 10,178 (47.8)          | 4,495 (47.5)           | 0.004   |
|   | Male                               | 15,736 (51.2)   | 10,969 (51.5)          | 4,767 (50.4)           |         |
|   | Twin/Triplet                       | 250 ( 0.8)      | 150 ( 0.7)             | 100 ( 1.1)             |         |
|   | Missing                            | 99 ( 0.3)       | 0 ( 0.0)               | 99 ( 1.0)              |         |
| Preterm Birth                                   | Term                               | 26,130 (85.0)   | 18,363 (86.2)          | 7,767 (82.1)           | <0.001  |
|   | Preterm                            | 4,628 (15.0)    | 2,934 (13.8)           | 1,694 (17.9)           |         |
| Gestational Age at outcome in weeks (Mean (SD)) |                                    | 39.4 (3.4)      | 39.5 (2.7)             | 39.2 (4.6)             | <0.001  |

Table S2-Comparing the Adjusted Risk Ratios for associations between risk factors and spontaneous preterm birth in different models

| Name of Variables                              | Categories                  | Model 1<br>Unadjusted Model<br><br>Risk Ratio<br>(95% CI) | Model 2<br>Adjusted Model<br>without<br>ANC/Place of<br>Delivery<br>(N=21,297)<br><br>Risk Ratio<br>(95% CI) | Model 3<br>Adjusted- Added<br>ANC<br>(N=19,965)<br><br>Risk Ratio<br>(95% CI) | Model 4<br>Adjusted- Added<br>ANC and Place<br>of Delivery<br>(N=19,964)<br><br>Risk Ratio<br>(95% CI) |
|--|-----------------------------|---|--|---|--|
| Maternal Age at LMP                            | 18 to 35                    | 1.00 [1.00,1.00]  | 1.00 [1.00,1.00]   | 1.00 [1.00,1.00]  | 1.00 [1.00,1.00]   |
|  | Less than 18                | 1.19*** [1.11,1.28]                                       | 1.13* [1.02,1.26]  | 1.11 [1.00,1.24]  | 1.11* [1.00,1.24]  |
|  | More than 35                | 1.57*** [1.36,1.81]                                       | 1.22 [0.98,1.51]   | 1.20 [0.97,1.49]  | 1.20 [0.97,1.49]   |
| Caste/Ethnicity Categories                     | Brahmin and Chhetri         | 1.00 [1.00,1.00]  | 1.00 [1.00,1.00]   | 1.00 [1.00,1.00]  | 1.00 [1.00,1.00]   |
|  | Vaishya                     | 1.33** [1.09,1.62]  | 1.23 [0.95,1.59]   | 1.19 [0.92,1.54]  | 1.20 [0.92,1.54]   |
|  | Shudra                      | 1.55*** [1.26,1.90]                                       | 1.23 [0.94,1.62]   | 1.18 [0.90,1.55]  | 1.18 [0.90,1.55]   |
|  | Muslim and others           | 1.96*** [1.60,2.42]                                       | 1.53** [1.16,2.01]   | 1.53** [1.16,2.01]  | 1.53** [1.16,2.02]   |
| Mother's Years of Education                    | No schooling                | 1.00 [1.00,1.00]  | 1.00 [1.00,1.00]   | 1.00 [1.00,1.00]  | 1.00 [1.00,1.00]   |
|  | 1 to 5 years                | 0.86** [0.78,0.95]  | 0.91 [0.80,1.03]   | 0.95 [0.83,1.08]  | 0.95 [0.83,1.08]   |
|  | More than 5 years           | 0.71*** [0.66,0.76]                                       | 0.81*** [0.73,0.90]  | 0.85** [0.77,0.95]  | 0.85** [0.76,0.94]   |
| Quintiles of Wealth                            | Poorest                     | 1.00 [1.00,1.00]  | 1.00 [1.00,1.00]   | 1.00 [1.00,1.00]  | 1.00 [1.00,1.00]   |
|  | Poorer                      | 0.86*** [0.79,0.93]                                       | 0.90* [0.82,1.00]  | 0.91 [0.83,1.01]  | 0.91 [0.83,1.01]   |
|  | Middle                      | 0.89** [0.82,0.96]  | 0.95 [0.86,1.05]   | 0.98 [0.88,1.08]  | 0.97 [0.88,1.08]   |
|  | Richer                      | 0.73*** [0.67,0.79]                                       | 0.83** [0.74,0.93]   | 0.88* [0.78,0.98]   | 0.87* [0.78,0.98]  |
|  | Richest                     | 0.71*** [0.65,0.77]                                       | 0.88* [0.78,1.00]  | 0.91 [0.80,1.03]  | 0.90 [0.80,1.02]   |
| Mother's height(centimeter)                    | <145                        | 1.00 [1.00,1.00]  | 1.00 [1.00,1.00]   | 1.00 [1.00,1.00]  | 1.00 [1.00,1.00]   |
|  | 145-<150                    | 0.93 [0.86,1.01]  | 0.98 [0.88,1.08]   | 0.98 [0.89,1.09]  | 0.99 [0.89,1.09]   |
|  | >=150                       | 0.81*** [0.75,0.87]                                       | 0.89* [0.81,0.98]  | 0.90* [0.82,1.00]   | 0.91 [0.82,1.00]   |
| Parity including both LB and SB, at Enrollment | Parity 1 to 4               | 1.00 [1.00,1.00]  | 1.00 [1.00,1.00]   | 1.00 [1.00,1.00]  | 1.00 [1.00,1.00]   |
|  | More than 4                 | 1.32*** [1.17,1.48]                                       | 1.17 [0.99,1.37]   | 1.11 [0.95,1.31]  | 1.12 [0.95,1.31]   |
|  | Prior Pregnant but parity 0 | 1.02 [0.85,1.22]  | 0.92 [0.62,1.37]   | 1.12 [0.73,1.73]  | 1.11 [0.72,1.72]   |
|  | No Prior Pregnant           | 1.10** [1.04,1.17]  | 1.15** [1.04,1.28]   | 1.20** [1.07,1.34]  | 1.19** [1.07,1.33]   |
| Interpregnancy Intervals                       | 18 to 36 months             | 1.00 [1.00,1.00]  | 1.00 [1.00,1.00]   | 1.00 [1.00,1.00]  | 1.00 [1.00,1.00]   |
|  | Less than 18 months         | 1.07 [0.99,1.14]  | 1.08 [0.99,1.18]   | 1.09 [0.99,1.19]  | 1.09 [0.99,1.19]   |
|  | More than 36 months         | 0.98 [0.89,1.09]  | 0.90 [0.79,1.02]   | 0.93 [0.82,1.06]  | 0.93 [0.82,1.06]   |
|  | No Prior Pregnancy          | 1.11** [1.03,1.20]  | 1.00 [1.00,1.00]   | 1.00 [1.00,1.00]  | 1.00 [1.00,1.00]   |
| Any death among prior LB                       | Prior LB but not died       | 1.00 [1.00,1.00]  | 1.00 [1.00,1.00]   | 1.00 [1.00,1.00]  | 1.00 [1.00,1.00]   |
|  | Prior LB died               | 1.19*** [1.09,1.29]                                       | 1.07 [0.97,1.19]   | 1.07 [0.96,1.20]  | 1.07 [0.96,1.20]   |
|  | Prior Pregnancy but no LB   | 1.07 [0.92,1.25]  | 1.06 [0.75,1.49]   | 0.97 [0.66,1.41]  | 0.96 [0.66,1.41]   |
|  | No prior pregnancy          | 1.12*** [1.06,1.19]                                       |  |   |  |

| Name of Variables   | Categories                         | Model 1<br>Unadjusted Model | Model 2<br>Adjusted Model<br>without<br>ANC/Place of<br>Delivery<br>(N=21,297) | Model 3<br>Adjusted- Added<br>ANC<br>(N=19,965) | Model 4<br>Adjusted- Added<br>ANC and Place<br>of Delivery<br>(N=19,964) |
|---|------------------------------------|-----------------------------|--|---|--|
|   |                                    | Risk Ratio<br>(95%CI)       | Risk Ratio<br>(95%CI)  | Risk Ratio<br>(95%CI)                           | Risk Ratio<br>(95%CI)  |
| Any prior pregnancy ended in SB                             | Prior pregnancy but no SB          | 1.00 [1.00,1.00]            |  |   |  |
|   | Prior SB                           | 1.08 [0.94,1.23]            |  |   |  |
|   | No prior pregnancy                 | 1.08** [1.02,1.15]          |  |   |  |
| Any prior pregnancy ended in miscarriage                    | Prior pregnancy but no miscarriage | 1.00 [1.00,1.00]            |  |   |  |
|   | Prior miscarriage                  | 0.94 [0.86,1.03]            |  |   |  |
|   | No prior pregnancy                 | 1.07* [1.01,1.13]           |  |   |  |
| Any prior pregnancy ended in multiples                      | Prior pregnancy but no multiples   | 1.00 [1.00,1.00]            |  |   |  |
|   | Prior multiples                    | 1.14 [0.87,1.49]            |  |   |  |
|   | No prior pregnancy                 | 1.08** [1.02,1.14]          |  |   |  |
| Number of ANC Visits  | No visit                           | 1.00 [1.00,1.00]            |  | 1.00 [1.00,1.00]                                | 1.00 [1.00,1.00]   |
|   | 1 visit                            | 0.98 [0.89,1.07]            |  | 1.00 [0.90,1.12]                                | 1.00 [0.90,1.12]   |
|   | 2-3 visit                          | 0.92* [0.85,0.99]           |  | 0.94 [0.86,1.03]                                | 0.93 [0.85,1.02]   |
|   | 4 or more                          | 0.54*** [0.50,0.59]         |  | 0.64***<br>[0.57,0.71]                          | 0.62***<br>[0.56,0.70]   |
| Place of Delivery   | Home/Maiti                         | 1.00 [1.00,1.00]            |  |   | 1.00 [1.00,1.00]   |
|   | HP/Clinic/Hospital                 | 0.84*** [0.79,0.89]         |  |   | 1.04 [0.96,1.12]   |
|   | Way to Facility/Outdoors           | 1.28** [1.09,1.51]          |  |   | 1.23 [1.00,1.52]   |
| Multiple Birth  | Singleton                          | 1.00 [1.00,1.00]            | 1.00 [1.00,1.00]   | 1.00 [1.00,1.00]                                | 1.00 [1.00,1.00]   |
|   | Twin/Triplet                       | 3.92*** [3.52,4.38]         | 4.91***<br>[4.20,5.75]   | 4.97***<br>[4.25,5.82]                          | 4.96***<br>[4.24,5.81]   |
| Sex of the Child  | Female                             | 1.00 [1.00,1.00]            | 1.00 [1.00,1.00]   | 1.00 [1.00,1.00]                                | 1.00 [1.00,1.00]   |
|   | Male                               | 1.10*** [1.04,1.17]         | 1.10** [1.02,1.17]   | 1.08* [1.01,1.16]                               | 1.08* [1.01,1.16]  |
|   | Twin/Triplet                       | 4.13*** [3.69,4.63]         | 1.00 [1.00,1.00]   | 1.00 [1.00,1.00]                                | 1.00 [1.00,1.00]   |
| STI in at least one visit of 2nd trimester?                 | No                                 | 1.00 [1.00,1.00]            |  |   |  |
|   | Yes                                | 0.99 [0.92,1.07]            |  |   |  |
| STI in at least one visit of 3rd trimester?                 | No                                 | 1.00 [1.00,1.00]            |  |   |  |
|   | Yes                                | 1.01 [0.92,1.12]            |  |   |  |
| Respiratory Problem in at least one visit of 2nd trimester? | No                                 | 1.00 [1.00,1.00]            | 1.00 [1.00,1.00]   | 1.00 [1.00,1.00]                                | 1.00 [1.00,1.00]   |
|   | Yes                                | 1.00 [0.94,1.06]            | 1.08 [1.00,1.16]   | 1.09* [1.01,1.18]                               | 1.09* [1.01,1.18]  |
| Respiratory Problem in at least one visit of 3rd trimester? | No                                 | 1.00 [1.00,1.00]            | 1.00 [1.00,1.00]   | 1.00 [1.00,1.00]                                | 1.00 [1.00,1.00]   |
|   | Yes                                | 0.85*** [0.79,0.92]         | 0.86** [0.79,0.94]   | 0.86** [0.78,0.94]                              | 0.86** [0.78,0.94]   |
| GI Problem in at least one visit of 2nd trimester?          | No                                 | 1.00 [1.00,1.00]            |  |   |  |
|   | Yes                                | 1.08 [0.98,1.18]            |  |   |  |
| GI Problem in at least one visit of 3rd trimester?          | No                                 | 1.00 [1.00,1.00]            |  |   |  |
|   | Yes                                | 1.04 [0.94,1.16]            |  |   |  |

| Name of Variables  | Categories          | Model 1<br>Unadjusted Model | Model 2<br>Adjusted Model<br>without<br>ANC/Place of<br>Delivery<br>(N=21,297) | Model 3<br>Adjusted- Added<br>ANC<br>(N=19,965) | Model 4<br>Adjusted- Added<br>ANC and Place<br>of Delivery<br>(N=19,964) |
|--|---------------------|-----------------------------|--|---|--|
|  |                     | Risk Ratio<br>(95%CI)       | Risk Ratio<br>(95%CI)  | Risk Ratio<br>(95%CI)                           | Risk Ratio<br>(95%CI)  |
| Poor appetite, nausea & vomiting in at least one visit of 2nd trimester?   | No                  | 1.00 [1.00,1.00]            | 1.00 [1.00,1.00]   | 1.00 [1.00,1.00]                                | 1.00 [1.00,1.00]   |
|  | Yes                 | 0.81*** [0.77,0.86]         | 0.86***<br>[0.80,0.92]   | 0.88***<br>[0.82,0.94]                          | 0.88***<br>[0.81,0.94]   |
| Poor appetite, nausea & vomiting in at least one visit of 3rd trimester?   | No                  | 1.00 [1.00,1.00]            | 1.00 [1.00,1.00]   | 1.00 [1.00,1.00]                                | 1.00 [1.00,1.00]   |
|  | Yes                 | 0.88** [0.82,0.95]          | 0.86***<br>[0.79,0.94]   | 0.87** [0.79,0.95]                              | 0.87** [0.79,0.95]   |
| Vaginal Bleeding in at least one visit of 2nd trimester?                   | No                  | 1.00 [1.00,1.00]            | 1.00 [1.00,1.00]   | 1.00 [1.00,1.00]                                | 1.00 [1.00,1.00]   |
|  | Yes                 | 0.91 [0.71,1.17]            | 0.84 [0.62,1.16]   | 0.83 [0.60,1.14]                                | 0.83 [0.60,1.15]   |
| Vaginal Bleeding in at least one visit of 3rd trimester?                   | No                  | 1.00 [1.00,1.00]            | 1.00 [1.00,1.00]   | 1.00 [1.00,1.00]                                | 1.00 [1.00,1.00]   |
|  | Yes                 | 1.44* [1.05,1.98]           | 1.53* [1.08,2.18]  | 1.49* [1.04,2.13]                               | 1.50* [1.04,2.15]  |
| Swelling in at least one visit of 2nd trimester?                           | No                  | 1.00 [1.00,1.00]            | 1.00 [1.00,1.00]   | 1.00 [1.00,1.00]                                | 1.00 [1.00,1.00]   |
|  | Yes                 | 1.32*** [1.12,1.55]         | 1.19 [0.98,1.46]   | 1.21 [0.98,1.48]                                | 1.21 [0.99,1.48]   |
| Swelling in at least one visit of 3rd trimester?                           | No                  | 1.00 [1.00,1.00]            | 1.00 [1.00,1.00]   | 1.00 [1.00,1.00]                                | 1.00 [1.00,1.00]   |
|  | Yes                 | 1.25** [1.09,1.44]          | 1.37***<br>[1.17,1.60]   | 1.36***<br>[1.15,1.60]                          | 1.36***<br>[1.15,1.60]   |
| High Systolic BP in one visit of 2nd trimester?                            | Normal Systolic BP  | 1.00 [1.00,1.00]            | 1.00 [1.00,1.00]   | 1.00 [1.00,1.00]                                | 1.00 [1.00,1.00]   |
|  | High Systolic BP    | 0.89 [0.59,1.34]            | 0.67 [0.40,1.12]   | 0.65 [0.39,1.09]                                | 0.65 [0.39,1.09]   |
| High Systolic BP in one visit of 3rd trimester?                            | Normal Systolic BP  | 1.00 [1.00,1.00]            | 1.00 [1.00,1.00]   | 1.00 [1.00,1.00]                                | 1.00 [1.00,1.00]   |
|  | High Systolic BP    | 1.92*** [1.52,2.41]         | 1.47* [1.08,2.01]  | 1.49* [1.08,2.07]                               | 1.49* [1.07,2.07]  |
| High Diastolic BP in one visit of 2nd trimester?                           | Normal diastolic BP | 1.00 [1.00,1.00]            | 1.00 [1.00,1.00]   | 1.00 [1.00,1.00]                                | 1.00 [1.00,1.00]   |
|  | High diastolic BP   | 1.34** [1.12,1.60]          | 1.09 [0.85,1.40]   | 1.06 [0.82,1.37]                                | 1.06 [0.82,1.38]   |
| High Diastolic BP in one visit of 3rd trimester?                           | Normal diastolic BP | 1.00 [1.00,1.00]            | 1.00 [1.00,1.00]   | 1.00 [1.00,1.00]                                | 1.00 [1.00,1.00]   |
|  | High diastolic BP   | 1.57*** [1.37,1.80]         | 1.41***<br>[1.17,1.70]   | 1.35** [1.12,1.64]                              | 1.35** [1.12,1.64]   |
| Average weight in 3rd trimester minus Average weight in 2nd trimester (kg) |                     | 0.88*** [0.87,0.90]         | 0.89***<br>[0.87,0.90]   | 0.89***<br>[0.87,0.90]                          | 0.89***<br>[0.87,0.90]   |

\*  $p < 0.05$ , \*\*  $p < 0.01$ , \*\*\*  $p < 0.001$