Preterm Birth and Cofactors of Survival Time and Time to First Hospitalization in Western Kenya

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Abstract

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Background

An estimated 10.6% of all births globally are preterm, rising to an estimated12% in sub-Saharan Africa. We evaluated the influence of preterm birth on infant mortality and time to first hospitalization in a birth cohort in Western Kenya.

Methods

This secondary analysis used data collected in a cluster randomized clinical trial on PrEP implementation strategies among HIV-negative women (PriMA, NCT#03070600). Women (N=4447) were enrolled during pregnancy at 20 antenatal care clinics in Western Kenya and mother-infant pairs were followed for 9 months postpartum. We used Kaplan-Meier and Cox regression to compare preterm and term infants for outcomes of death, first hospitalization, and first hospitalization or death, and to identify correlates of these outcomes both in the general population and among preterm infants.

Results

Among 4107 deliveries, 7350 (17.8%) were preterm (PTB). PTB was associated with 4.43-fold increased risk of hospitalization (95% confidence interval [CI]: 2.19, 8.95) and a higher likelihood of neonatal mortality than term births (2.5% versus 1.4% p=0.045). Overall, the majority of first hospitalizations and deaths occurred within the first week of life among both preterm and term infants, and risk of first hospitalization was associated PTB, lower gestational age, and household crowding. Among preterm infants, male sex, lower gestational age and longer travel time to clinic (HR 3.56 [1.12, 11.34]) were associated with higher risk of first hospitalization. Lower maternal social support, and partner positive or unknown HIV status, were associated with decreased risk of mortality and first hospitalization.

Conclusion

Preterm birth, lower gestational age, low birth weight, and male sex were associated with increased risk of hospitalization and mortality. Among preterm infants, social context influenced likelihood of mortality. Targeted interventions to facilitate timely medical attention and address maternal support may improve outcomes for preterm infants.

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Introduction

Preterm birth is defined by the World Health[1] Organization as a live birth prior to 37 completed weeks of gestational age. Worldwide, an estimated 15 million infants, or an estimated 10.6% of infants are born preterm annually, with rates increasing over time in many countries[2]. Complications related to preterm birth (PTB) are the leading cause of death of children under 5 worldwide[3]. Preterm birth is known to be strongly associated with adverse outcomes among neonates and infants as well as with increased risk of chronic disease throughout the life course. Preterm birth is more prevalent in low-income countries, and especially prevalent in Southeast Asia and Sub-Saharan Africa, where 60% of all preterm births are estimated to occur[4]. In Kenya, approximately 12% of all live births are PTB[4,5], with an estimated 13,300 children under 5 dying of complications directly related to preterm birth annually[6].

In addition to global disparities in risk of preterm birth, there are notable disparities in outcomes among preterm birth infants. Very preterm infants (born prior to 32 weeks of gestation) generally require specialized care. In low-income settings, half of very preterm infants die[1]. The vast majority of these deaths could be prevented with access to appropriate care[1]. Appropriate care includes warmth, breastfeeding and nutritional support, and treatment for infections and respiratory problems, and can have a substantial impact on morbidity and mortality. Prior research on the experiences of caregivers of preterm infants in western Kenya has identified community support and access to support from healthcare workers as important factors that may optimize outcomes for these infants[7].

Although preterm birth is well-established as a risk factor for adverse neonatal and infant outcomes, patterns, timing and cofactors of mortality and hospitalizations among preterm infants are less well characterized. Care practices that improve preterm infant outcomes, including kangaroo care, breastfeeding, WASH practices, and prompt care-seeking for illnesses or infections depend on caregiver support, education, and resources at home[3]. This study aims to estimate the impact of preterm birth on infant death and hospitalization, and to identify correlates of mortality and hospitalization among preterm infants – particularly the impact of psychosocial factors.

Methods:

Study design and setting: The current report is from a nested prospective study which used data from a cluster-randomized controlled trial (RCT) evaluating HIV pre-exposure prophylaxis (PrEP) implementation strategies in Kenya (PrIMA Study, NCT# 03070600) in Kenya.

Study population and study procedure: PrIMA was conducted in 20 antenatal care clinics in Western Kenya, in the Siaya and Homa Bay counties, in areas with HIV seroprevalence higher than 20%. The PrIMA study enrolled participants between January 2018 and June 2019. Clinics eligible for inclusion in the RCT offered both antenatal and postnatal care services and had more than 350 HIV-negative clients attending prenatal care annually. The 2014 Kenya Demographic and Health Survey (DHS) estimated ANC attendance to be 96% among women aged 15-49 who gave birth between 2009 and 2014[8], thus, ANC attendees were likely a representative sample of pregnant people within the clinics' catchment areas. The study sites were selected to ensure geographic distribution, with the 20 sites dispersed over 300 km. All study sites in the parent RCT study were included in this analysis. Participants in the PrIMA study were HIV-negative pregnant women receiving care at the participating ANC clinics. Eligibility requirements included: not already using PrEP, age of at least 15 years, plans to reside in the area for at least 1 year postpartum and receive postnatal and infant care at the study facility, tuberculosis negative, and not participating in any other studies concurrently.

All data were collected by trained study nurses at participating ANC clinics as part of the PrIMA study, using table-based standardized survey instruments and a REDCap database and data abstracted from medical records. Multiple survey instruments were used across several consecutive study visits – some data was collected during pregnancy (enrollment and monthly visits until delivery), 6 weeks, 14 weeks, 6 months, and 9 months postpartum. Maternal demographic information and social support information was collected during pregnancy. Gestational age at birth was estimated using either last menstrual period [LMP] or fundal height at enrollment, and date of delivery.

Ethical Review: The parent study was reviewed and approved by University of Washington Institutional Review Board and Kenyatta National Hospital Ethical Review Committee. All participating women provided written informed consent.

Outcomes of Interest: Infant death, first infant hospitalization, or first infant hospitalization or death were the outcomes of this analysis.

Time to infant death was defined as the number of days between recorded date of birth and recorded date of death. Time to first hospitalization was defined as the number of days between the recorded date of birth and the earliest recorded date of hospitalization, with a time to first hospitalization of zero days for infants who were hospitalized without being discharged after birth Time to death or first hospitalization was defined as the number of days between the recorded date of birth and the earliest date for either hospitalization or death.

Participants were considered lost to follow-up if they did not have an endpoint of either death, hospitalization or survival to 9 months postpartum. Lost to follow-up date was the midpoint between the last client visit the participant attended and the next scheduled visit the participant did not attend. In time-to-first-hospitalization analyses, infants who died but were never hospitalized were censored at death. For time-to-event analyses, only the first 270 days of follow-up after the date of birth were considered. Missing data were imputed using information found in serious adverse event (SAE) reports where available (n=2), and otherwise using the following methods:

For infants who were recorded as having been hospitalized and who died within five days of birth, but did not have a recorded hospitalization date (n=12), hospitalization date was imputed to be the date of birth.

For infants who were recorded as having been hospitalized and later died, for whom the hospitalization date is missing and the date of death is more than five days after the date of birth (n=12), the date of hospitalization was imputed using the average time difference between hospitalization and death dates among all participants who had both outcomes and were not missing either date. This average was 2 days, so the missing hospitalization dates were filled in to be two days earlier than the recorded dates of death

For infants who were missing dates of birth, but who had recorded dates of death and were specifically listed as neonatal deaths (n=4), date of birth was imputed from the average age of neonatal death in the dataset (5 days). For infants missing both date of birth and date of death, but for whom the death was recorded as neonatal (n=2), the time to mortality was imputed directly, using the same method.

For infants missing date of death who were not specifically recorded as neonatal or non-neonatal deaths (n=2), date of death was imputed using the average number of days from birth to death among all infants who died (32 days)

Exposures of Interest: Preterm birth (PTB) was defined as an estimated gestational age at birth (estimated using last menstrual period [LMP] or fundal height at enrollment) of less than 37 weeks. Within preterm births, we additionally evaluated differences by each week of gestational age at birth. Key evaluated covariates for mortality and hospitalization included maternal demographics and psychosocial factors as well as infant characteristics. Maternal demographic factors included age at enrollment, years of school completed, marital and employment status, travel time to the ANC clinic in hours, household crowding (number of people per household room), partner HIV status, partner age difference, and maternal STI history. Standardized questionnaires were used to assess psychosocial factors at baseline. Social support was assessed using the Medical Outcomes Survey Social Support Survey (MOS SSS)[9]. Intimate partner violence (IPV) was assessed using the HITS scale[10], and dichotomized at a cutoff of 10, as well as around the presence or absence of any reported physical violence at any time during the study period. Maternal depression was assessed using the Patient Health Questionnaire 2 (PHQ 2)[11], and dichotomized at a PHQ-2 score of 3. Additional exposures included maternal STIs during the course of the pregnancy, infant sex, and infant birth weight.

Statistical Methods:

Descriptive Analysis

Proportions and medians of cofactors of interest (described above) for both the overall study population and by PTB status were summarized. For each cofactor and outcome of interest, a two-sided t-test (for continuous variables) or chi-squared test (for categorical variables) was used to determine whether there was a statistically significant ($\alpha = 0.05$) difference between term and PTB infants.

Distribution of Outcomes

Incidence of infant mortality, infant hospitalization, and infant mortality or hospitalization were compared by PTB status. The median survival time among those who died or were hospitalized was estimated using Kaplan-Meier curves.

Correlates of mortality and hospitalization among all infants

Time to first hospitalization, time to death, and time to first hospitalization or death analyses of all live singleton births and of all live singleton preterm births were performed using Cox regression models. Multivariable models included PTB status as well as any covariates that were found to have an association that was significant at the 0.1 level. In cases where multiple measures of the same covariate (eg: both the continuous variable "number of people per room in household" and the binary variable "more than two people per room in household") were found to be significant, only one measure was included. (Figures 2a-c; Tables 2a-c). Since the parent study was a cluster-RCT, all models were clustered by facility. A similar approach was used to conduct stratified analyses of correlates of mortality or hospitalization among PTB Infants (Figures 3a-c; Tables 3a-c). The threshold for significance of results was p= 0.05.

All analyses were conducted in R 4.1.2.(R Core Team 2021)

Results:

Baseline comparison of mother-infant pairs with PTB and term births

Among 4,107 mother-infant pairs included in this analysis (92.3% of participants enrolled in the parent PrIMA cRCT), 730 (17.8%) infants were preterm. Median gestational age at birth was 38 weeks (interquartile range [IQR] 2) among term infants and 36 weeks (IQR 0) among preterm infants. Median maternal age at enrollment was 24 years (IQR 7.36); 84.6% of participants were married; and, 14.8% were employed. The median travel time to the clinic was 30 minutes (IQR 35), and the median number of people per room in participants households was 1.67 (IQR 1.5). Few (1.2%) mothers reported having been previously treated for an STI, and 1.2% tested positive for syphilis during the study. Overall, 11.6% of 3877 mothers who had a current sexual partner either knew their partner to have tested positive for HIV or did not know their partner's HIV status, and 41.1% of participants were determined to be at high risk for HIV infection using a standardized risk assessment[12]. Mothers of PTB infants had a slightly lower education and shorter travel time to clinic than mothers of term infants (mean of 10.1 years vs 10.3 years, p=0.044, and mean of 37.9 minutes vs 40.2 minutes, p=0.016, respectively). Mothers with PTB infants had significantly lower median social support (77 vs 80, p<0.001). PTB infants were less likely to be male than term infants (44.2% vs. 48.9%, p=0.041). Other maternal demographics did not differ significantly between term and PTB infants.

<u>Incidence of mortality, hospitalization and mortality or hospitalization</u>

As presented in Table 2, PTB infants had higher risk of death, hospitalization, and death or hospitalization than term infants, with incidence of mortality of 2.51 deaths per 100 person-years (py) among term infants and 4.05 deaths per 100 py among preterm infants (p= 0.24 for difference), incidence of first hospitalization of 0.89 per 100 py among term infants and 3.39 per 100 py among preterm infants ($p=5.6 * 10^{-6}$ for difference), and incidence of first event (either death or hospitalization) of 2.93 per 100 py among term infants and 4.96 per 100 py among preterm infants (p=0.04 for difference). Unadjusted Kaplan-Meier survival curves (Figure 2a-c) also show a significant difference in times to both hospitalization and death or hospitalization, as well as a notable but not statistically significant difference in time to death.

<u>Correlates of risk of death, hospitalization, or either in the overall cohort</u>

Univariate analyses estimating the associations between potential cofactors and time to infant death, infant hospitalization, or infant death or hospitalization in the entire cohort are summarized in Table 3. Higher gestational age at birth was protective for risk of all three outcome measures, with estimated hazard ratios (HR) for each additional week of gestational age at birth of 0.84 [95%

confidence interval [CI]: 0.74, 0.95], 0.74 [95% CI: 0.66, 0.82], and 0.82 [095% CI: 0.72, 0.92] for death, hospitalization, and combined outcomes respectively. PTB was significantly associated 4.21-fold increased risk of hospitalization (HR 4.21, 95% CI 2.11, 8.38}. Higher birthweight was substantially protective for mortality with a 64% decrease in mortality risk per additional kg of birthweight (HR 0.36, 95% CI 0.16, 0.80). There was a trend for increased risk of mortality for PTB infants compared to term infants, (HR 1.64, 95% CI 0.88, 3.06) and for hospitalization or death (HR 1.78, 95% CI 0.99, 3.20}. There were trends for associations of increased risk with maternal marriage - however, these did not reach statistical significance. Household crowding of greater than 2 people per room was associated with an increased hazard of mortality (HR 1.56, 95% CI 1.00, 2.44) and combined outcomes (HR 1.54, 95% CI 1.03, 2.32). Male infants had increased risk of mortality (HR 2.06, 95% CI 1.00, 4.27).

Correlates of mortality, hospitalization or either among PTB infants

Table 5 contains a summary of univariate analyses of cofactors for mortality, hospitalization, and death or hospitalization among preterm infants. Among PTB infants, gestational age at birth was significantly associated with protective effect on mortality, hospitalization or either, (HR 0.75, 95% CI 0.66, 0.85, HR 0.71, 95% CI 0.63, 0.81, and HR 0.72, 95% CI 0.65, 0.80 for death, hospitalization, and combined outcomes, respectively). Longer travel time to the clinic was significantly associated with increased risk of hospitalization per minute (HR 1.01 95% CI 1.00, 1.03). There was also a trend for increased risk for mortality with longer travel time (HR 1.01, 95% CI 1.00, 1.02) as well as for combined outcomes (HR 1.01, 95% CI 1.00, 1.03). Travel time to clinic of >30 minutes was \ significantly associated with an over 3-fold higher risk of hospitalization (HR 3.56, 95% CI 1.12, 11.34) and similar non-significant trends were present for mortality and combined outcomes (HR 2.31, 95% CI 0.73, 7.31 and HR 2.30, 95% CI 0.96, 5.54 respectively). Each additional point on the social support scale was significantly associated with an increased risk of mortality and combined outcomes (HR 1.04 95% CI 1.00, 1.09 and HR 1.04 95% CI 1.00, 1.08). Male infants had a significantly >3-fold higher risk of mortality than female infants (HR 3.15, 95% CI1.06, 9.40). Higher birthweight was associated with a significantly decreased risk of hospitalization and combined outcomes (HR 0.12, 95% CI 0.03, 0.59) for each additional kilogram of birthweight. Additionally, there was a trend towards an association between any reported physical intimate partner violence during the study period and lower risk of hospitalization or death (HR 0.53, 95% CI 0.28, 1.02).

Multivariate analyses of cofactors of mortality, hospitalization, or either among PTB infants

Multivariate analyses included all covariates associated with each outcome at p< 0.1, excluding redundant variables and birthweight and infant sex, which had high missingness among preterm infants (Table 1). In the multivariate model for time to mortality, each additional week of gestational age was strongly associated with a decreased risk (HR 0.74, 95% CI 0.66, 0.83). Each additional minute of travel time to clinic and each additional point on the social support scale were significantly associated with increased risk (HR 1.01, 95% CI 1.00, 1.02 and HR 1.04, 95% CI 1.01, 1.08). Gestational age at birth (HR 0.69, 95% CI 0.60, 0.80), positive or unknown partner HIV status (HR 0.97, 95% CI 0.95, 1.00), and travel time to clinic (HR 1.02, 95% CI 1.00, 1.03) remained significantly associated with risk of hospitalization. In the multivariate model for the combined outcomes, longer travel time to the clinic and higher maternal social support score remained significantly associated with increased risk (HR 1.01, 95% CI 1.00, 1.03 and 1.04, 95% CI 1.01, 1.08), while higher gestational age was strongly associated with lower risk (HR 0.69, 95% CI 0.63, 0.76)

Discussion:

In this large multi-site cohort in Western Kenya, 17.8% of infants were preterm. During 9-month postpartum follow-up, PTB infants had a significantly higher cumulative incidence of death, hospitalization or the combined outcome than term infants. Three percent of PTB infants died by 9 months of age and 3.7% were either hospitalized or died in this period, unacceptably high incidence. Overall, higher gestational age of infants at birth was highly protective for these outcomes among both the general population and preterm infants. The majority of deaths and hospitalizations occurred during the neonatal period among both the general population and preterm infants, with the trend most pronounced among preterm infants. PTB, low gestational age or low birthweight were substantial contributors to first hospitalization or mortality in the general population, with limited influence of other cofactors, except for male sex and household crowding, while several other social factors were significantly associated with mortality or hospitalization among preterm infantsThese data underscore the large impact of PTB on infant outcomes.

While there is strong evidence that PTB increases risk of morbidity and mortality in general, to date, few studies have elucidated cofactors of mortality and hospitalization among PTB infants. Among PTB infants, cofactors of mortality included gestational age at birth, infant sex, and reported maternal social support, and of hospitalization included gestational age, partner HIV status, travel time to clinic, and birth weight. In the general population, only gestational age at birth, birth weight, infant sex, and household crowding are significant cofactors. Overall, these findings suggest that healthcare access and social factors have an increased impact on preterm birth infants.

We found higher mortality for male infants, low birth weight infants, and infants with lower gestational age - both in the general study population and among preterm birth infants specifically, with male sex and gestational age having stronger effects among preterm infants. These findings are consistent with prior research. Male infants have been reported to have an overall higher rate of infant mortality than female infants[13]. Previous studies among preterm have also observed higher rates of death and adverse outcomes in male infants[14,15]. Speculated reasons for excess male mortality risk in PTB infants include sex-specific differences in fetal lung development and immune response, which are exacerbated by lower gestational age at birth[14, 15]. Low birth weight and preterm birth have also been consistently found to be strongly associated with infant mortality and serious adverse outcomes, with each additional week of prematurity having the greatest effect among infants who are most premature[3].

In addition to these risk factors present in both the general population and the preterm population, several social covariates were significantly associated with adverse outcomes only among preterm infants. Counterintuitively, we found maternal social support was inversely related to hospitalization and mortality in the cohort among PTB infants. Studies on the influence of social support on PTB have employed a variety of social support measures, making direct comparisons difficult. However, in general, higher maternal social support has been found to be associated with better birth outcomes[16], or with known protective factors (such as adequate gestational age and birth weight[17] or delivery in a clinic[18]), so our finding was surprising. It is unclear what is driving the association we observed. Possibilities include an association between social support and another risk factor, such as economic status, in our study population, or difficulty early in pregnancy leading to more social support. Partner HIV positive or unknown status was protective for hospitalization among preterm birth infants. This at-risk group may have been expected to have poorer outcomes and it is unclear why outcomes were better, although one possibility is increased contact with healthcare services and associated support. Generally, both the social support and partner HIV status likely measure social factors that may influence PTB outcomes. Household crowding was associated with increased hospitalization and mortality overall, but these associations were not present among preterm birth infants, suggesting that socioeconomic and household support structures impact preterm and term infants differently, although the exact mechanism is unclear

We found that travel time to clinic was associated with a higher risk of hospitalization and either death or hospitalization, as well non-significantly increased risk of death among preterm infants.

This suggests that preterm infants are particularly vulnerable to differences in ease of access to care, a finding consistent with research on the impact of appropriate neonatal medical care for preterm infants[3]. Difficulty in travelling to local clinics may be a significant barrier to accessing needed care for this population. While distance to clinic may also reflect socioeconomic status, measures of household crowding, a proxy for socioeconomic status, did not correlate with travel time. Due to the timing of adverse events, which tended to occur shortly after birth, with many hospitalizations and deaths within the first day, it is clear that this difference includes difficulty in accessing care during or before the time of birth. Travel time to clinic of greater than 30 minutes was the social factor with the largest effect size on risk of all the assessed outcomes, and is the most immediately promising avenue for pursuing targeted interventions.

Strengths of our study included the large sample size, prospective and longitudinal data collection, and the data on many potential cofactors not previously studied in connection with outcomes for preterm infants in this population. This study also on a population with high rates of both infant mortality and preterm birth by both global and national standards, where effective interventions to improve outcomes for preterm infants are urgently needed.

An important limitation of the study is the exploratory and non-experimental design of this secondary analysis – while associations of interest can be identified, the causal mechanisms behind them can't be definitively determined by this study. In some cases, such as with maternal social support, the results are counterintuitive, and more study is required to determine what is driving the association. Another limitation is that, despite the very large sample size, the outcomes of interest are rare enough that study power remains a concern. In addition, a few variables of interest, including infant sex and birthweight, had significant missingness, making performing analyses including these variables somewhat difficult. This study may not be generalizable to communities with different social and economic dynamics, or to populations with major differences in antenatal care coverage and access.

The results of this study align with the existing literature on the risks associated with preterm birth, infant sex, and birthweight, while also indicating that several social factors are particularly significant for preterm infants. Most notably, travel time of greater than 30 minutes is associated with a dramatic increase in hazard for preterm infants, suggesting improving access to healthcare for vulnerable mothers and infants living far from clinics as an especially crucial area for future research and targeted interventions to ultimately improve outcomes for preterm infants

Tables and Figures:

Figure 1: Inclusion Flow Diagram

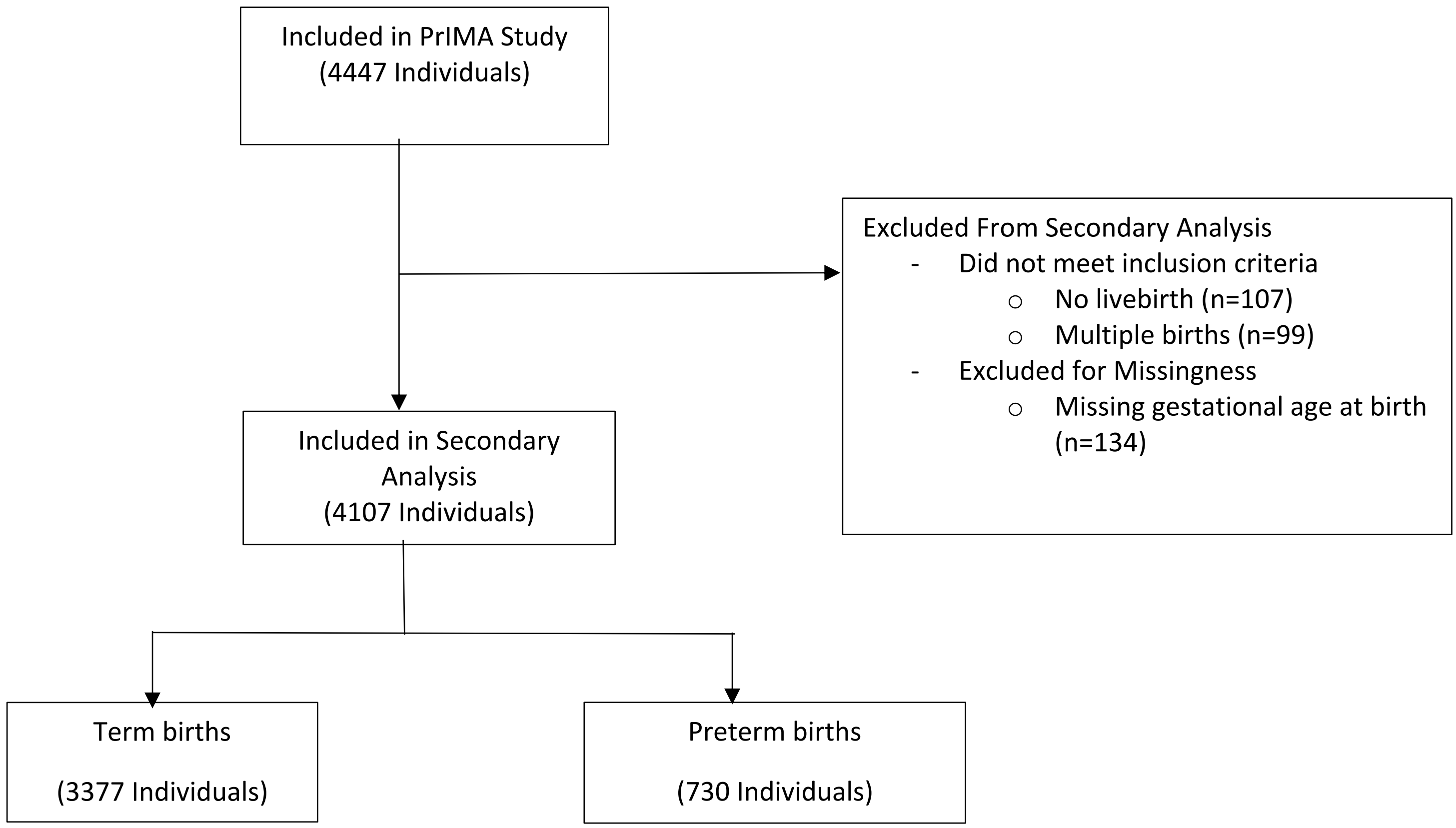

Table 1: Baseline characteristics of term and preterm infants at birth

	Total N= 4107 Median (IQR) or n (%)	Term infants N= 3377 Median (IQR) or n (%)	Preterm infants N= 730 Median (IQR) or n (%)	p-Value
Maternal sociodemographics				
Maternal age (years)	24.0 (7.36)	24.0 (7.42)	23.9 (7.08)	0.103
Maternal years of school	10.0 (4.00)	10.0 (4.00)	10.0 (4.00)	0.044
Maternal marital status (n= 4060), ref: not married	3436 (84.6%)	2830 (84.9%)	606 (83.5%)	0.369
Maternal employment status (n=4041), ref: not employed	601 (14.9%)	492 (14.8%)	109 (15.1%)	0.87
Travel time to clinic (minutes)	30.0 (35.0)	30.0 (30.0)	30.0 (25.0)	0.0156
Household crowding score	1.67 (1.50)	1.67 (1.50)	1.67 (1.25)	0.968
Household crowding score >2 (n = 4064)	1956 (47.6%)	1603 (47.5%)	353 (48.4%)	0.77
Maternal social support score	80.0 (27.0)	80.0 (27.0)	77.0 (30.0)	<0.001
High HIV Risk				
Partner HIV status (n= 3877)				
HIV-positive or unknown	379 (11.57%)	319 (%)	60 (%)	0.319
HIV-negative	3498 (88.43%)	2867 (%)	631 (%)	
Maternal history of STI (n=4092)	51 (1.2%)	47 (1.4%)	4 (0.5%)	0.0913
Positive maternal syphilis test (n=4019)	48 (1.2%)	43 (1.4%)	5 (0.7%)	0.268
Maternal HITS score >10 (n= 3948)	309 (7.8%)	266 (8.2%)	43 (6.1%)	0.0743
Any reported physical IPV (n= 4107)	1913 (46.6%)	1567 (46.4%)	346 (47.4%)	0.654
Partner age difference >10 years (n= 2675)	481 (18.0%)	403 (16.3%)	78 (14.0%)	0.194
Maternal PHQ-2 score > 3 (n= 3696)	351 (9.5%)	283 (9.4%)	68 (10.0%)	0.672
Infant Characteristics				
Infant sex male (n= 3459)	1662 (48.0%)	1390 (48.9%)	272 (44.2%)	0.0406
Gestational age at birth (weeks)	38.0 (2.00)	38.0 (2.00)	36.0 (0.00)	<0.001
Birth weight (kg)	3.4 (0.60)	3.4 (0.65)	3.2 (0.50)	<0.001
Low birth weight (n= 2661)	60 (2.3%)	38 (1.7%)	22 (4.8%)	<0.001

p-Value determined by chi-squared test (for counts) or t test (for continuous variables) comparing term and preterm infants

Table 2. Outcomes of preterm and term infants

Total0 N=4107	Term infants N= 3377	Preterm infants N= 730	p-value
Infant death during follow-up	61 (1.8%)	21 (2.9%)	0.087
Neonatal death (within first 28 days)	46 (1.4%)	18 (2.5%)	0.045*
Deaths per 100 person-years	2.51	4.05	0.244
First percentile survival time (days) [95% CI]	6 [2, 27]	0 [0, 5]	
Median survival time (days) among infants with outcome [95% CI]	5 [2, 14]	1 [0,23]	
Hospitalization during follow-up	22 (0.7%)	18 (2.5%)	<0.0001*
First hospitalizations per 100 person-years	0.89	3.39	<0.0001*
First percentile time to first hospitalization [95% CI]	NA	0 [0, 0]	
Median days to first hospitalization among infants with outcome [95% CI]	6 [1, 38]	0 [0, 0]	
Infant death or hospitalization during follow-up	71 (2.1%)	26 (3.6%)	0.028*
First percentile time (days) to first hospitalization or death [95% CI]	3 [1, 13]	0 [0, 0]	
Median days to first infant hospitalization or death among infants with outcome [95% CI]	4 [2, 12]	0 [0, 0]	
Incidence of first hospitalization or death per 100 person-years	2.93	4.96	0.042*

Figure 1a. Comparison of time to mortality between preterm and term infants

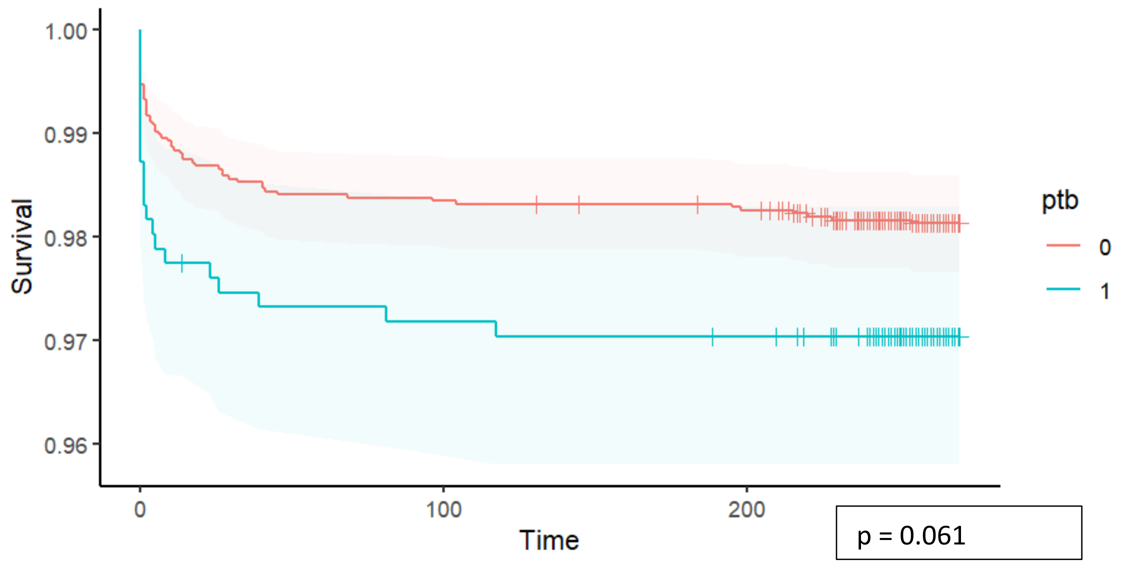

Figure 1b . Comparison of time to hospitalization between preterm and term infants

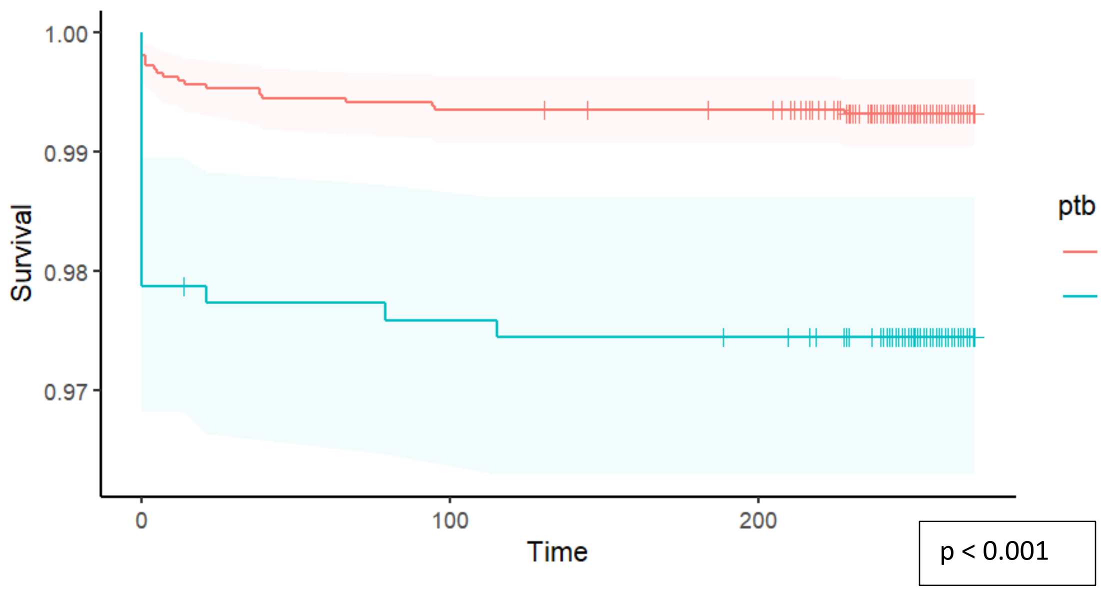

Figure 1c. Comparison of time to first hospitalization or death (combined outcome) between preterm and term infants

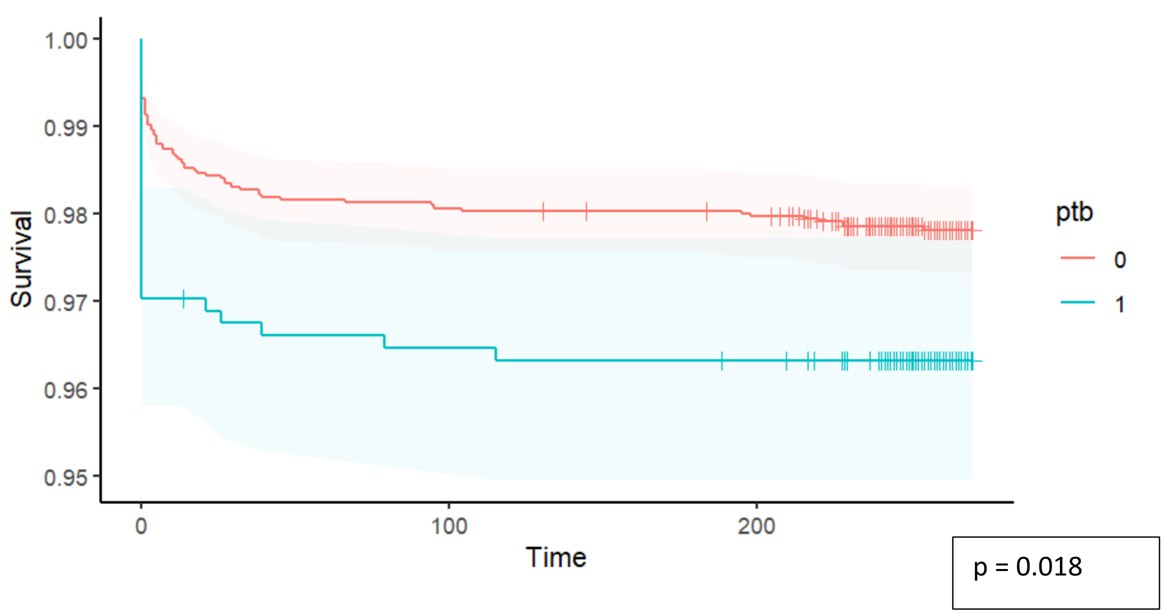

Table 3: Univariate cofactors of mortality and hospitalization among singleton livebirths

	COFACTORS OF MORTALITY			**COFACTORS OF HOSPITALIZATION**			**COFACTORS OF HOSPITALIZATION OR DEATH**		
Factor	Hazard Ratio	95% confidence interval	p-value	Hazard Ratio	95% confidence interval	p-value	Hazard Ratio	95% Confidence Interval	p-value
Preterm birth	1.64	0.88, 3.06	0.122	**4.21**	**2.11, 8.38**	**<0.0001***	**1.78**	**0.99, 3.20**	**0.052**
Maternal Sociodemographics									
Maternal age (years)	1.03	0.98, 1.08	0.346	1.02	0.97, 1.06	0.520	1.03	0.99, 1.08	0.157
Maternal years of school	0.98	0.92, 1.04	0.502	1.05	0.95, 1.17	0.372	1.00	0.94, 1.07	0.953
Maternal marital status reference: not married	1.99	1.00, 3.97	**0.050**	3.21	0.75, 13.90	0.117	**2.05**	**0.89, 4.76**	**0.093**
Maternal employment reference: not employed	0.74	0.36, 1.39	0.345	1.18	0.41, 3.37	0.753	0.98	0.50, 1.91	0.954
Travel time to clinic (minutes)	1.03	0.99, 1.01	0.499	1.01	1.00, 1.01	**0.066**	1.00	0.99, 1.01	0.863
Travel time to clinic > 30	0.90	0.53, 1.51	0.678	1.55	0.77, 3.12	0.222	0.93	0.61, 1.40	0.721
Household crowding (people/room)	1.04	0.96, 1.13	0.289	0.94	0.63, 1.40	0.759	1.05	0.97, 1.14	0.222
High household crowding (>2 people/room)	1.56	1.00, 2.44	**0.049***	0.82	0.46, 1.54	0.533	1.54	1.03, 2.32	**0.038***
High HIV risk	1.11	0.64, 1.93	0.707	0.62	0.31, 1.25	0.182	1.05	0.66, 1.66	0.853
Partner HIV positive or unknown, ref: partner HIV negative	1.00	1.00, 1.01	0.676	1.00	0.97, 1.02	0.840	1.00	0.99, 1.01	0.939
Maternal STI history	1.07	0.14, 8.06	0.949	NA			0.89	0.12, 6.72	0.911
Maternal syphilis	NA			NA			NA		
Maternal social support score	1.01	0.99, 1.02	0.286	1.02	0.99, 1.05	0.174	1.01	0.99, 1.03	0.195
Maternal HITS score >10	0.89	0.34, 2.35	0.814	0.67	0.17, 2.60	0.563	0.89	0.34, 2.33	0.813
Any physical IPV	0.83	0.55, 1.23	0.353	0.82	0.50, 1.33	0.411	0.79	0.56, 1.12	0.181
Maternal partner age difference >10 years	1.30	0.76, 2.23	0.335	1.23	0.48, 3.12	0.667	1.29	0.73, 2.25	0.380
Maternal PHQ-2 Score > 3	1.17	0.60, 2.27	0.644	1.32	0.38, 4.54	0.663	1.30	0.70, 2.42	0.408

Infant Characteristics									
Infant sex male	**2.06**	**1.00, 4.27**	**0.050**	1.63	0.86, 3.08	0.133	1.45	0.86, 2.44	0.165
Gestational age at birth (weeks)	**0.84**	**0.74, 0.95**	**0.004***	**0.74**	**0.66, 0.82**	**<0.0001***	**0.82**	**0.72, 0.92**	**0.001***
Birth weight (kg)	**0.36**	**0.16, 0.80**	**0.013***	0.33	0.05, 2.08	0.238	0.34	0.08, 1.33	0.120

Table 4: Multivariate cofactors of mortality and hospitalization among singleton livebirths

	COFACTORS OF MORTALITY			**COFACTORS OF HOSPITALIZATION**			**COFACTORS OF HOSPITALIZATION OR DEATH**		
Factor	Hazard Ratio	95% confidence interval	p-value	Hazard Ratio	95% confidence interval	p-value	Hazard Ratio	95% Confidence Interval	p-value
Preterm birth	1.58	0.84, 2.99	0.159	3.97	2.04, 7.74	**<0.0001***	1.74	0.96, 3.14	**0.066**
Maternal Sociodemographics									
Maternal marital status reference: not married	2.02	1.00, 4.07	**0.050**		--------------		2.09	0.89, 4.89	**0.091**
Travel time to clinic > 30 minutes		--------------		1.59	0.77, 3.31	0.211			
Household crowding > 2	1.56	1.00, 2.43	**0.049***	0.78	0.41, 4.13	0.432	1.54	1.02, 2.31	**0.038***

Table 5: Cofactors of mortality and hospitalization among preterm livebirths – summary of univariate analyses

	COFACTORS OF MORTALITY			**COFACTORS OF HOSPITALIZATION**			**COFACTORS OF MORTALITY OR HOSPITALIZATION**		
Factor	Hazard Ratio	95% confidence interval	p-Value	Hazard Ratio	95% confidence interval	p-Value	Hazard Ratio	95% Confidence Interval	p-Value
Gestational age (weeks)	0.75	0.66, 0.85	**<0.0001***	0.71	0.63, 0.81	**<0.0001***	0.72	0.65, 0.80	**<0.0001***
Maternal Sociodemographics									
Maternal age (years)	1.02	0.98, 1.09	0.584	1.02	0.96, 1.08	0.514	1.04	0.99, 1.09	0.139
Maternal years of school	1.05	0.95, 1.22	0.478	1.10	0.90, 1.36	0.350	1.11	0.96, 1.28	0.158
Maternal marital status reference: not married		*NA – zero cell*			*NA – zero cell*			*NA – zero cell*	
Maternal employment status reference: not employed	1.13	0.34, 3.68	0.843	1.29	0.34, 4.95	0.706	1.66	0.54, 5.12	0.375
Travel time to clinic (minutes)	1.01	1.00, 1.02	**0.092**	1.01	1.00, 1.03	**0.013***	1.01	1.00, 1.03	**0.056**
Travel time to clinic > 30 minutes	2.31	0.73, 7.31	0.154	3.57	1.12, 11.34	**0.031***	2.30	0.96, 5.54	**0.062**
Household crowding score (people/room)	0.72	0.45, 1.14	0.164	0.90	0.49, 1.64	0.722	0.87	0.54, 1.39	0.551
High household crowding (>2 people/room)	0.67	0.27, 1.63	0.372	0.73	0.25, 2.16	0.571	0.96	0.39, 2.39	0.928
High HIV Risk	0.82	0.28, 2.42	0.717	0.68	0.27, 1.69	0.407	0.89	0.36, 2.16	0.790
Partner HIV positive or unknown, ref: partner HIV negative	0.96	0.89, 1.03	0.232	0.98	0.96, 1.00	**0.024***	0.97	0.95, 0.99	**0.016***
Maternal STI history		*NA – zero cell*			*NA – zero cell*			*NA – zero cell*	
Maternal positive syphilis test		*NA – zero cell*			*NA – zero cell*			*NA – zero cell*	
Maternal social support score	1.04	1.00, 1.09	**0.034***	1.03	0.99,1.07	0.111	1.04	1.00, 1.08	**0.028***
Maternal HITS score >10		*NA – zero cell*			*NA – zero cell*			*NA – zero cell*	
Any reported physical IPV	0.62	0.32, 1.21	0.162	0.68	0.31, 1.48	0.332	0.53	0.28, 1.02	**0.058**
Maternal partner age difference >10 years	0.38	0.08, 1.80	0.223	0.88	0.30, 2.62	0.821	0.61	0.18, 2.08	0.443
Maternal PHQ-2 Score > 3	0.53	0.06, 4.84	0.572	0.64	0.09, 4.69	0.662	0.95	0.22, 4.06	0.944
Infant Characteristics									

Infant sex male	3.15	1.06, 9.40	**0.040***	1.76	0.61, 5.09	0.295	1.76	0.61, 5.09	0.295
Birth weight (kg)	*NA – missingness*			0.12	0.03, 0.59	**0.009***	0.12	0.03, 0.59	**0.009***

Table 6: Cofactors of mortality and hospitalization among preterm livebirths – multivariate analyses

	COFACTORS OF MORTALITY			**COFACTORS OF HOSPITALIZATION**			**COFACTORS OF MORTALITY OR HOSPITALIZATION**		
Factor	Hazard Ratio	95% confidence interval	p-Value	Hazard Ratio	95% confidence interval	p-Value	Hazard Ratio	95% Confidence Interval	p-Value
Gestational age (weeks)	0.74	0.66, 0.83	**<0.0001***	0.69	0.60, 0.80	**<0.0001***	0.69	0.63, 0.76	**<0.0001***
Maternal Sociodemographics									
Travel time to clinic (minutes)	1.01	1.00,1.02	**0.026***	1.02	1.00, 1.03	**0.003***	1.01	1.00, 1.03	**0.007***
Partner HIV status positive or unknown		-------------		0.97	0.95, 1.00	**0.019***	0.95	0.88, 1.03	0.204
Maternal social support score	1.04	1.01, 1.08	**0.019***		--------------		1.04	1.01, 1.08	**0.017***
Any reported physical IPV		--------------			--------------		0.46	0.20, 1.08	**0.073**

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