A comprehensive array of adverse reproductive events and risk of preterm birth: new insights from the Boston Birth Cohort

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Abstract

Preterm birth (PTB) is an important public health issue. A suite of biomedical and social factors, including history of adverse reproductive events, increase the risk of PTB. Existing studies on adverse reproductive events and PTB mainly focus on one type of adverse reproductive event. Few examined a comprehensive array of them. In this study, we aim to investigate the association between a comprehensive array of adverse reproductive events and PTB. Applying logistic and logit regressions, we find significant bivariate association between any adverse reproductive events/stillbirth/miscarriage and PTB. However, their associations attenuate after we adjust other confounders with one exception. That is the number of miscarriage is still significantly associated with PTB. Specifically, each one additional miscarriage is associated with a 6% higher risk of PTB. Possible biological mechanisms and the study limitations and strengths are discussed. Similar studies applying population representative pregnancy registry data could be an improved next step.

Introduction

Preterm births (PTB) complications are the leading cause of child mortality in the US and globally.[1,2] In the US, the burden of PTB is increasing due to high rates of PTB and improved survival of very PTB babies. At present, PTB affects 1 in 9 births and 1 in 6 African American births, and persistent racial disparities remain.[3-5] If survived, children born prematurely could suffer from many short- and long-term complications, e.g. neonatal respiratory distress and cerebral palsy.[3, 6]

A suite of biomedical and social factors increase the risk of PTB. Those include history of PTB, abortions, race, and neighborhood poverty.[3, 6-13] Despite mounting evidence, PTB is still largely unpredictable.[3] Identifying women at high-risk of PTB is important because it is a critical step to prevent PTB. More research is urgently needed to better understand the primary causes of PTB.[3] Institute of Medicine recommended to "investigate the etiologies of PTB" and "study the multiple psychosocial, behavioral, and environmental risk factors associated with PTB simultaneously".[3] The recommendations highlight the significance of the application of interdisciplinary approaches to investigate the joint effects of social and biomedical risk factors. Indeed, risk factors of PTB may accumulate longitudinally through the life course of women's reproductive career given their social, economic and demographic background. In this study, we apply an interdisciplinary approach to understand the joint effects of biomedical and social etiologies of PTB. Specifically, we seek to examine the effects of a comprehensive array of adverse reproductive events on PTB by applying the life course framework.

Applying the life course perspective to women's reproductive career, risk factors and outcomes of previous pregnancies could accumulate in a complex manner to influence the outcomes of subsequent pregnancies.[14] Reproductive health is a continuum. Age at menarche, menstrual cycle pattern, spontaneous abortion, induced abortion, or stillbirth may all influence the risk of PTB. Empirical evidence supports this theory, showing that history of PTB, spontaneous abortion, and induced abortion all increase the risk of PTB.[3, 9] However, most studies examined these adverse pregnancies individually, but few considered a comprehensive array of them together. In addition, previous studies often ignored the correlated nature of reproductive events within the same women, potentially leading to biased statistical inference.[15]

We aim to fill these gaps by tracking women's adverse reproductive events from age at menarche, taking advantage of the extensive data on PTB collected in the Boston Birth Cohort. We answer the following research questions. Does adverse reproductive events increase the risk of PTB? If so, what types of adverse reproductive events and how much do they increase the risk of PTB? Does the number of adverse reproductive events matter? Does multiple types of adverse reproductive events further increase the risk of PTB? Will these differ between multiparous vs. nulliparous women?

Methods

Study data

Boston Birth Cohort has been enrolling women at the Boston Medical Center since October 1998. Boston Medical Center is a large urban hospital with a predominantly minority, inner-city patient population.[16] The BBC was set up to study PTB, hence women with PTB were over-sampled. Out of the 8,494 births collected in BBC thus far, 2,311 were PTB and 3,579 were the first live births (mothers of whom were nulliparous).

The study outcome is whether a live birth is preterm, defined as a live birth occurred before 37 weeks of gestational age. Gestational age here was determined by "the first day of the last menstrual period and early prenatal ultrasonographic results".[16] The PTB status was extracted from electronic medical records and further distinguished into spontaneous PTB and medically indicated PTB.

The risk factor of interest is a comprehensive array of adverse reproductive events. Information on adverse reproductive events was collected up to 12 pregnancies before the index pregnancy captured by BBC. The information was collected based on retrospective self-reports using a standardized questionnaire. Measures of general characteristics of a woman's reproductive cycle, including age at menarche and menstrual regularity are available. In addition, gestational age, pregnancy complications, type of delivery, and presence of congenital abnormalities, and types of adverse reproductive events (i.e. live birth, stillbirth, miscarriage, induced abortion, moles and ectopic pregnancy) are also available for each of the 12 pregnancies. Other known risk factors of PTB were extensively measured in BBC and are adjusted in the analyses.

Statistical analyses

We conducted systematic data cleaning. Missing data is a non-trivial issue because we rely on women's self-reports of their history of adverse reproductive events. What is often missing is the date when these events occurred. However, in this study, we only use an indication (whether or not it happened) or the number of each event. Thus even though exact date of each event was missing, we assume that such reported events occurred. This minimizes the impact of the missingness. For additional missing data, e.g. those among known risk factors of PTB which we adjust in the regressions, we used k-Nearest Neighbor imputation provided in R package VIM[17] and present the regression results without and with imputation. The underlying assumption of this approach is such that the distribution of the known risk factor is similar among those missing and non-missing.

Ideally, we would line up all adverse reproductive events chronologically and apply longitudinal data analysis techniques to analyze the data. However, we are not able to do so because we have a lot of missing data on when the adverse pregnancy

events occur. Instead we chose a regular logistic regression. But in addition to derive odds ration (OR) through the logistic regression, we also derived relative risk (RR) through a logit regression. The reason we also derived RR is that it is a commonly accepted measure for risk. The OR is often calculated because it is a convenient parameter in logistic regression. It is widely understood that OR is approximately the same as RR if the prevalence rate of the condition under investigation is very small (for rare event). But there could be a non-ignorable difference between these two measures when the event is not rare. The condition under investigation in our study is PTB, and it is not rare. In fact, because of the over sampling design of the Boston Birth Cohort, the PTB prevalence in this study dataset is 27%. Therefore, we estimated both RR and OR in this study.

To derive RR for continuous variable (e.g. reproductive time, age), confounders' values are fixed to mean. For binary confounders (e.g. menstrual regularity, hypertension), their values are set to zero. And for nominal confounders (e.g. race, education), their values are set to their reference level. The confidence interval of RR is derived using bootstrapping.

Through the regressions, we examined the following associations: 1) association between any adverse reproductive event and PTB; 2) association between a specific type of adverse reproductive event and PTB; 3) association between number of adverse reproductive events and PTB; and 4) association between two or more adverse reproductive events and PTB. All the analyses were done separately for nulliparous and multiparous women as initial exploration of the data suggests that different associations exist when comparing the two groups of women.

We used Akaike's An Information Criterion to select all a set of confounders included in the model for nulliparous and multiparous women and using R package glmulti,[18] we could automatically compare all possible models and find the best models in terms of smallest AIC values.

We plan to also conduct the following stratified analyses and sensitivity analyses:

- Stratified analyses
    - By PTB subtypes: i.e. spontaneous versus medically indicated PTB
    - By age groups: <20, 20-34, 35+
    - By race, and
    - By gender of the baby
- Sensitivity analyses
    - Excluding imputed cases
    - Retrospective study design often oversamples women with very short or very long reproductive life span. Therefore we will exclude these outliers (e.g. those <15y or >50y) to minimize the oversampling issue.

Results

A total of 2,496 out of 3,493 nulliparous women and 3,185 out of 4,594 multiparous women were included in the analysis.

Webappendix tables 1 and 2 show the bivariate association between PTB and known risk factors among nulliparous and multiparous women, respectively. No missing imputation is included in these two tables and the extent of missingness by risk factor is reported. Overall, as expected, most known risk factors are associated with PTB.

Tables 1 and 2 present the bivariate association between PTB and adverse reproductive events among nulliparous and multiparous women, respectively. Here imputation to address missingness has been included. We find that any reported adverse reproductive event, miscarriage, and the number of miscarriage are all associated with increased risk of PTB among both nulliparous and multiparous women. However, stillbirths and number of stillbirths are only robustly associated (i.e. both OR and RR are statistically significant) with PTB among multiparous women.

Tables 3 and 4 show the adjusted association between preterm births and adverse reproductive event among nulliparous and multiparous women, respectively. Imputation to address missingness is included here. No robust statistical association is identified among nulliparous women between adverse reproductive events and PTB after known confounds are adjusted. Among multiparous women, the number of miscarriage is still statistically significant (OR: 1.07, 95% confidence interval (1.00, 1.17); RR: 1.06, 95% confidence interval (1.00, 1.14)) after controlling for confounders. Specifically, for each one more miscarriage women reported, they are at a 6% higher risk of having a subsequent PTB. No combination of two events is statistically significant.

Discussion

We find significant bivariate association between any adverse reproductive events/stillbirth/miscarriage and PTB. However, their associations attenuate after we adjust other confounders with one exception. That is the number of miscarriage is still significantly associated with PTB. Each one additional miscarriage is associated with a 6% higher risk of PTB.

Previous studies suggest that there could be several possible biological mechanisms linking miscarriage and PTB. First, inflammation state from miscarriage could trigger maternal or fetal hypothalamic-pituitary-adrenal (HPA) axis that led to the subsequent PTB.[19, 20] Second, cervical trauma, cervical incompetence, or changes in the cervicovaginal flora after miscarriage could play a role.[21-23] Lastly, miscarriage and PTB may be both rooted in placental issues.

The study is subject to a number of limitations. First, the number of adverse reproductive events is not particularly large. Given the number of cases and the

amount of confounders adjusted, we speculate that our models may be over-saturated. We will further investigate this issue. Second, our adverse reproductive events are based on retrospective self-reports. Such measures are subject to recall bias and suffer from missing data issues. We did conduct imputation to try to alleviate the missingness. Results are not qualitatively different with and without imputed cases. Third, the study population is urban minority population. Hence the results have limited external validity. To systematically address these issues, a large representative population study using pregnancy registry data could be an improved next step.

Meanwhile, the study has a few strengths. Different from previous studies, this study examines a comprehensive array of adverse reproductive events. In addition, we also considered length of reproductive life span and menstrual regularity, which was not previously done. Lastly, we have good measures of PTB based on electronic medical records.

Additional studies examining reproductive history as a whole are needed to confirm the study finding. Biomarkers can be integrated into the analyses to further control known risk factors of PTB. If the study results can be replicated elsewhere, obstetricians should be advised to provide counseling to their patients who have had a history of miscarriage on heightened PTB risk. Relevant health management approaches should also be advised. Clearly, to reduce PTB, it is critical to prevent and minimize adverse reproductive events. To achieve this goal, demographic (e.g. promote modern family planning use and minimize unintended pregnancies) and health (e.g. timely management of intrauterine infection) preventions can be used.

Tables and Figures

Table 1. Bivariate association between preterm births and adverse reproductive events among nulliparous women, with imputation

Variables	Full term (N=2531)	Preterm (N=962)		
	% or mean	% or mean	Odds ratio	Relative risk (baseline = 0)
Indication of any adverse pregnancy	27.93	34.41	1.35 (1.14, 1.57)	1.24 (1.11, 1.38)
Indication of stillbirth	0.32	1.35	4.32 (0.50, 8.14)	2.26 (1.46, 3.00)
Indication of miscarriage	12.96	20.17	1.70 (1.36, 2.03)	1.44 (1.27, 1.63)
Indication of abortion	17.19	18.09	1.06 (0.86, 1.27)	1.05 (0.91, 1.21)
Indication of ectopic	0.99	0.83	0.84 (0.17, 1.51)	0.88 (0.38, 1.47)
Number of stillbirth	0.00	0.01	4.21 (0.58, 7.85)	2.24 (1.52, 3.03)
Number of miscarriage	0.18	0.30	1.37 (1.21, 1.53)	1.25 (1.16, 1.37)
Number of abortion	0.23	0.25	1.05 (0.92, 1.18)	1.04 (0.95, 1.13)
Number of ectopic	0.01	0.01	0.75 (0.23, 1.26)	0.80 (0.42, 1.21)

Table 2. Bivariate association between preterm births and adverse reproductive events among multiparous women, with imputation

Variables	Full term (N=3319)	Preterm (N=1275)		
	% or mean	% or mean	Odds ratio	Relative risk (baseline = 0)
Indication of any adverse pregnancy	47.36	54.75	1.34 (1.17, 1.52)	1.24 (1.13, 1.37)
Indication of stillbirth	2.74	4.55	1.69 (1.12, 2.26)	1.42 (1.11, 1.73)
Indication of miscarriage	26.66	34.82	1.47 (1.27, 1.67)	1.31 (1.20, 1.44)
Indication of abortion	25.46	27.22	1.09 (0.93, 1.25)	1.07 (0.96, 1.18)
Indication of ectopic	1.99	1.96	0.99 (0.53, 1.44)	0.99 (0.68, 1.34)
Number of stillbirth	0.03	0.05	1.50 (1.05, 1.93)	1.32 (1.04, 1.59)
Number of miscarriage	0.36	0.53	1.30 (1.19, 1.40)	1.20 (1.14, 1.28)
Number of abortion	0.40	0.44	1.05 (0.98, 1.14)	1.04 (0.98, 1.10)
Number of ectopic	0.02	0.02	0.95 (0.55, 1.35)	0.96 (0.66, 1.25)

Table 3. Adjusted[1] association between preterm births and adverse reproductive event among nulliparous women, with imputation

Variables	Full term (N=2,531)	Preterm (N=962)		
	% or mean	% or mean	Odds ratio	Relative risk
Indication of any adverse pregnancy	27.93	34.41	1.11 (0.92, 1.31)	1.08 (0.95, 1.22)
Indication of stillbirth	0.32	1.35	2.10 (0.03, 4.17)	1.64 (0.84, 2.77)
Indication of miscarriage	12.96	20.17	1.25 (0.97, 1.52)	1.17 (1.00, 1.38)
Indication of abortion	17.19	18.09	1.01 (0.80, 1.23)	1.01 (0.85, 1.18)
Indication of ectopic	0.99	0.83	0.73 (0.09, 1.37)	0.79 (0.26, 1.40)
Number of stillbirth	0.00	0.01	2.13 (0.14, 4.13)	1.66 (0.90, 2.71)
Number of miscarriage	0.18	0.30	1.11 (0.96, 1.26)	1.08 (0.99, 1.19)
Number of abortion	0.23	0.25	1.00 (0.86, 1.13)	1.00 (0.90, 1.10)
Number of ectopic	0.01	0.01	NA	NA
Indication of stillbirth x miscarriage	0.00	0.01	NA	NA
Indication of miscarriage x abortion	0.03	0.05	1.06 (0.52, 1.60)	1.04 (0.66, 1.49)
[2]Indication of stillbirth vs no APH[3]	0.44[4]	2.02	2.17 (1.97, 2.36)	1.68 (0.85, 2.85)
Indication of miscarriage vs no APH	15.24	23.52	1.25 (1.02, 1.48)	1.18 (0.99, 1.39)
Indication of abortion vs no APH	19.26	21.61	1.05 (0.76, 1.35)	1.04 (0.87, 1.22)

[1]Adjusted confounders include reproductive time, menstrual regularity, general life stress, intrauterine infection, pregnancy-induced hypertension, cervix incompetency, illicit drug use, alcohol use, family support, and receipt of public assistance. Their inclusion is based on the best regression fit using Akaike's An Information Criterion.

[2]Here we consider three-level categorical exposure variable either (1) indication of stillbirth, (2) no adverse pregnancy history at all, and (3) any adverse pregnancy history other than stillbirth. Same for miscarriage and abortion.

[3]APH = adverse pregnancy history

[4]Proportion of stillbirth in history among the women who have never had adverse pregnancy history other than stillbirth. Same for miscarriage and abortion.

Table 4. Adjusted[1] association between preterm births and adverse reproductive events among multiparous women, with imputation

Variables	Full term (N=3,319)	Preterm (N=1,275)	Odds ratio	Relative risk (preterm history = 0)	Relative risk (preterm history = 1)
	% or mean	% or mean			
Indication of any adverse pregnancy	47.36	54.75	1.01 (0.86, 1.15)	1.01 (0.88, 1.15)	1.00 (0.90, 1.12)
Indication of stillbirth	2.74	4.55	1.39 (0.88, 1.91)	1.34 (0.92, 1.80)	1.26 (0.95, 1.59)
Indication of miscarriage	26.67	34.82	1.13 (0.96, 1.31)	1.12 (0.98, 1.27)	1.09 (0.97, 1.21)
Indication of abortion	25.46	27.22	0.86 (0.72, 1.00)	0.87 (0.76, 1.01)	0.90 (0.78, 1.01)
Indication of ectopic	1.99	1.96	0.94 (0.46, 1.42)	0.95 (0.55, 1.47)	0.96 (0.60, 1.31)
Number of stillbirth	0.03	0.05	1.26 (0.85, 1.66)	1.22 (0.92, 1.64)	1.17 (0.90, 1.46)
Number of miscarriage	0.36	0.53	1.08 (0.99, 1.18)	1.07 (1.00, 1.17)	1.06 (1.00, 1.14)
Number of abortion	0.40	0.44	0.93 (0.85, 1.01)	0.94 (0.87, 1.01)	0.95 (0.89, 1.01)
Number of ectopic	0.02	0.02	0.91 (0.49, 1.33)	0.92 (0.54, 1.36)	0.93 (0.60, 1.28)
Indication of stillbirth x miscarriage	0.01	0.01	0.69 (0.14, 1.25)	0.78 (0.32, 1.61)	0.75 (0.33, 1.37)
Indication of miscarriage x abortion	0.07	0.11	1.19 (0.89, 1.60)	1.17 (0.87, 1.56)	1.13 (0.91, 1.40)
[2]Indication of stillbirth vs no APH[3]	4.95[4]	9.13	1.38 (1.24, 1.53)	1.33 (0.96, 1.83)	1.26 (0.94, 1.63)
Indication of miscarriage vs no APH	33.62	43.49	1.09 (0.92, 1.26)	1.08 (0.93, 1.25)	1.06 (0.94, 1.20)
Indication of abortion vs no APH	32.60	37.55	0.89 (0.69, 1.09)	0.90 (0.77, 1.05)	0.92 (0.80, 1.05)

[1]Adjusted confounders include reproductive time, indication of preterm birth in history, general life stress, intrauterine infection, pregnancy-induced hypertension, gestational diabetes mellitus, cervix incompetency, smoking experience, body mass index, and receipt of public assistance. Their inclusion is based on the best regression fit using Akaike's An Information Criterion.

[2]Here we consider three-level categorical exposure variable either (1) indication of stillbirth, (2) no adverse pregnancy history at all, and (3) any adverse pregnancy history other than stillbirth. Same for miscarriage and abortion.

[3]APH = adverse pregnancy history

[4]Proportion of stillbirth in history among the women who have never had adverse pregnancy history other than stillbirth. Same for miscarriage and abortion.

References

1. Li Liu, Shefali Oza, Dan Hogan, Yue Chu, Jamie Perin, Jun Zhu, Joy Lawn, Simon Cousens, Colin Mathers, Robert E. Black. 2016. “Global, regional and national causes of child mortality in 2000-2015 – implications for the Sustainable Development Goals” Lancet. Published online on November 10, 2016

2. Centers for Disease Control, National Center for Health Statistics, National Vital Statistics System. “10 Leading Causes of Death by Age Group, United Sates - 2014”. Available at: http://www.cdc.gov/injury/images/lc-charts/leading_causes_of_death_age_group_2014_1050w760h.gif (accessed on September 29, 2016)

3. Committee on Understanding Premature Birth and Assuring Healthy Outcomes. 2007. PTB: Causes, Consequences, and Prevention. Richard E. Behrman, Adrienne Stith Butler, Editors. The Institute of Medicine of the National Academies. The National Academies Press. Washington DC

4. Centers for Disease Control and Prevention. Preterm Birth. Available from: http://www.cdc.gov/reproductivehealth/maternalinfanthealth/pretermbirth.htm/ (accessed July 10,2015)

5. March of Dimes. 2014 Premature Birth Report Card. Available from: http://www.marchofdimes.org/materials/premature-birth-report-card-united-states.pdf (accessed July 10,2015)

6. Wang G, Divall S, Radovick S, Paige D, Ning Y, Chen Z, Ji Y, Hong X, Walker SO, Caruso D, Pearson C, Wang MC, Zuckerman B, Cheng TL, Wang X. Preterm birth and random plasma insulin levels at birth and in early childhood. JAMA: the journal of the American Medical Association. 2014;311:587-596

7. Shah PS; Knowledge Synthesis Group on Determinants of LBW/PT births. “Parity and low birth Iight and PTB: a systematic review and meta-analyses” Acta Obstet Gynecol Scand. 2010 Jul;89(7):862-75. doi: 10.3109/00016349.2010.486827

8. Cnattingius S1, Villamor E, Johansson S, Edstedt Bonamy AK, Persson M, Wikström AK, Granath F. “Maternal obesity and risk of preterm delivery” JAMA. 2013 Jun 12;309(22):2362-70. doi: 10.1001/jama.2013.6295

9. Watson LF1, Rayner JA, King J, Jolley D, Forster D, Lumley J. “Modelling prior reproductive history to improve prediction of risk for very preterm birth” Paediatr Perinat Epidemiol. 2010 Sep;24(5):402-15. doi: 10.1111/j.1365-3016.2010.01134.x

10. Blumenshine P1, Egerter S, Barclay CJ, Cubbin C, Braveman PA. “Socioeconomic disparities in adverse birth outcomes: a systematic review” Am J Prev Med. 2010 Sep;39(3):263-72. doi: 10.1016/j.amepre.2010.05.012

11. Li Liu, Ting Chen, Yuelong Ji, Lingxin Hao, Xiaobin Wang. 2016 “The effects of perceived psychosocial stress and maternal medical conditions on preterm births: empirical evidence from the Boston Birth Cohort”. To be presented at the 2017 Annual Meeting of Population Association of America (poster), Chicago, April 2017

12. Pathik D. Wadhwa, Sonja Entringer, Claudia Buss, and Michael C. Lu. “The Contribution of Maternal Stress to Preterm Birth: Issues and Considerations” Clin Perinatol. 2011 Sep; 38(3): 351–384. doi: 10.1016/j.clp.2011.06.007

13. Wallace, M.; Harville, E.; Theall, K.; Ibber, L.; Chen, W.; Berenson, G. Neighborhood poverty, allostatic load, and birth outcomes in African American and white women: Findings from the Bogalusa Heart Study. Health Place 2013, 24, 260–266.

14. Kuh,D. and Ben-Shlomo, Y. (2004) A Life Course Approach to Chronic Disease Epidemiology: Tracing the Origins of Ill-health from Early to Adult Life, 2nd edn. Oxford: Oxford University Press

15. De Stavola BL, Nitsch D, dos Santos Silva I, McCormack V, Hardy R, Mann V, Cole TJ, Morton S, Leon DA. “Statistical issues in life course epidemiology” Am J Epidemiol. 2006 Jan 1;163(1):84-96. Epub 2005 Nov 23

16. Wang X, Zuckerman B, Pearson C, et al. Maternal cigarette smoking, metabolic gene polymorphism, and infant birth weight. JAMA. 2002 Jan 9; 287(2):195–202. [PubMed: 11779261]

17. Kowarik, Alexander, and Matthias Templ. "Imputation with the R Package VIM." Journal of Statistical Software 74.7 (2016): 1-16.

18. Calcagno, V., & de Mazancourt, C. (2010). glmulti: an R package for easy automated model selection with (generalized) linear models. Journal of statistical software, 34(12), 1-29

19. Henriet, L., & Kaminski, M. (2001). Impact of induced abortions on subsequent pregnancy outcome: the 1995 French national perinatal survey. BJOG, 108(10), 1036-4102

20. Moreau, C., Kaminski, M., Ancel, P., Bouyer, J., Escande, B., Thiriez, G., . . . Larroque, B. (2005). Previous induced abortions and the risk of very preterm delivery: results of the EPIPAGE study. BJOG, 112(4), 430-437. doi:10.1111/j.1471-0528.2004.00478.x

21. Swingle, H., Colaizy, T., Zimmerman, M., & Morriss, F. J. (2009). Abortion and the risk of subsequent preterm birth: a systematic review with meta-analyses. J Reprode Med, 54(2), 95-108

22. Ankum, WM., Waard, MW.-d., & Bindels, PJ. (2001). Management of spontaneous miscarriage in the first trimester: an example of putting informed shared decision making into practice. BMJ, 322(7298), 1343–1346

23. Hogue, C., Cates, WJ., & Tietze, C. (1982). The effects of induced abortion on subsequent reproduction. Epidemiol Rev, 4, 66-94

Webappendix:

Webappendix table 1. Bivariate association between preterm births and established risk factors with missingness among nulliparous women

Variables	Full term (N=2531)	Preterm (N=962)	Odds ratio	Relative risk (baseline = 0 or mean)	Missing (%)
	% or mean	% or mean			
Reproducible time (yr)	12.29	13.10	1.02 (1.01, 1.04)	1.02 (1.01, 1.03)	1.75
Menstrual regularity	86.19	81.78	0.72 (0.58, 0.86)	0.79 (0.70, 0.92)	0.72
Perceived psychosocial stress (z-score)					
General life stress	0.65	0.76	1.31 (1.15, 1.46)	1.22 (1.12, 1.32)	0.72
Stress during pregnancy	0.76	0.86	1.21 (1.09, 1.33)	1.15 (1.07, 1.25)	0.60
Major maternal medical conditions					
Intrauterine infection	16.79	23.86	1.55 (1.27, 1.84)	1.37 (1.22, 1.53)	1.03
Pregnancy-induced hypertension	8.47	25.68	3.73 (2.98, 4.49)	2.26 (2.04, 2.52)	1.40
Gestational diabetes mellitus	3.98	6.87	1.81 (1.21, 2.42)	1.49 (1.19, 1.80)	8.76
Other maternal characteristics, also add delivery mode					
Age	25.06	25.74	1.02 (1.01, 1.03)	1.02 (1.01, 1.03)	0.00
Race					
Black	30.23	33.37	1.15 (0.97, 1.33)	1.11 (0.99, 1.24)	0.00
White	13.59	14.76	1.10 (0.87, 1.33)	1.07 (0.90, 1.25)	0.00
Hispanic	27.87	24.32	0.83 (0.69, 0.97)	0.87 (0.76, 0.98)	0.00
Others	28.09	27.55	0.97 (0.81, 1.13)	0.98 (0.87, 1.10)	0.00
Cervix Incompetency	0.68	6.48	10.18 (4.66, 15.70)	2.98 (2.58, 3.34)	0.60
Maternal education					
Lower than high school	30.01	28.94	0.95 (0.79, 1.10)	0.96 (0.85, 1.08)	1.57
High School or GED	30.63	33.54	1.14 (0.96, 1.32)	1.10 (0.98, 1.23)	1.57
Some college or above	39.30	37.71	0.93 (0.78, 1.07)	0.95 (0.85, 1.07)	1.57
Illicit drug use	20.83	27.02	1.41 (1.16, 1.65)	1.27 (1.13, 1.43)	3.18
Alcohol use (from before 6 month of pregnancy)	34.37	30.68	0.85 (0.71, 0.98)	0.88 (0.79, 0.99)	2.61
Ever smoke	16.55	20.94	1.34 (1.08, 1.59)	1.23 (1.07, 1.41)	0.72

Maternal BMI	24.71	25.46	1.02 (1.01, 1.03)	1.02 (1.01, 1.03)	6.58
Family support	2.45	2.40	0.90 (0.80, 1.01)	0.93 (0.88, 1.02)	6.33
Receipt of public assistance	7.35	13.52	1.98 (1.49, 2.45)	1.57 (1.35, 1.81)	4.38

Webappendix table 2. Bivariate association between preterm births and established risk factors with missingness among multiparous women

Variables	Full term (N=3319)	Preterm (N=1275)	Odds ratio	Relative risk (baseline = 0 or mean)	Missing (%)
	% or mean	% or mean			
Reproducible time (yr)	17.00	18.23	1.03 (1.02, 1.05)	1.03 (1.02, 1.04)	2.66
Preterm birth history	15.28	37.64	3.35 (2.85, 3.84)	2.21 (2.03, 2.42)	0.00
Menstrual regularity	89.11	87.53	0.86 (0.69, 1.03)	0.90 (0.79, 1.04)	0.85
Perceived psychosocial stress (z-score)					
General life stress	72.09	83.66	1.30 (1.17, 1.43)	1.21 (1.13, 1.31)	0.81
Stress during pregnancy	80.89	92.63	1.24 (1.13, 1.35)	1.17 (1.09, 1.25)	0.76
Major maternal medical conditions					
Intrauterine infection	8.68	21.31	2.85 (2.33, 3.37)	1.97 (1.79, 2.17)	0.78
Pregnancy-induced hypertension	7.99	25.08	3.86 (3.16, 4.55)	2.29 (2.07, 2.51)	2.00
Gestational diabetes mellitus	7.28	9.56	1.35 (1.03, 1.66)	1.23 (1.04, 1.45)	6.38
Other maternal characteristics, also add delivery mode					
Age	30.07	31.10	1.03 (1.02, 1.04)	1.03 (1.01, 1.04)	0.00
Race					
Black	32.96	35.22	1.11 (0.96, 1.26)	1.07 (0.98, 1.18)	0.00
White	9.58	11.22	1.19 (0.94, 1.44)	1.13 (0.97, 1.29)	0.00
Hispanic	30.28	26.98	0.85 (0.73, 0.97)	0.89 (0.80, 1.00)	0.00
Others	27.18	26.59	0.97 (0.83, 1.11)	0.98 (0.83, 1.11)	0.00
Cervix Incompetency	1.36	5.92	4.57 (2.85, 6.28)	2.34 (2.00, 2.68)	0.33
Maternal education					
Lower than high school	33.23	32.88	0.98 (0.85, 1.12)	0.98 (0.89, 1.08)	2.24
High School or GED	33.88	37.64	1.18 (1.02, 1.34)	1.12 (1.02, 1.23)	2.24
Some college or above	32.89	29.48	0.85 (0.73, 0.97)	0.89 (0.80, 0.98)	2.24
Illicit drug use	18.90	26.13	1.52 (1.28, 1.75)	1.34 (1.20, 1.49)	3.77
Alcohol use (from before 6 month of pregnancy)	26.43	28.51	1.11 (0.95, 1.27)	1.08 (0.97, 1.20)	2.96
Ever smoke	17.89	26.52	1.66 (1.40, 1.91)	1.42 (1.28, 1.56)	0.89
Maternal BMI	26.75	26.84	1.00 (0.99, 1.01)	1.00 (0.99, 1.01)	7.14

Family support	2.33	2.34	1.03 (0.93, 1.13)	1.02 (0.95, 1.10)	7.55
Receipt of public assistance	7.71	12.58	1.72 (1.35, 2.09)	1.45 (1.25, 1.64)	4.72