Estimation of the causal effect of sex on neonatal intensive care unit outcomes among very low birth weight infants

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Abstract

Objective: Estimate the causal effect of sex on outcomes in the neonatal intensive care unit (NICU) among very low birth weight (VLBW) infants.

Study Design: Retrospective cohort study comparing NICU outcomes for VLBW males versus females. Odds ratios (OR) for outcomes that differed significantly by sex were computed using standard unweighted analysis and inverse probability weighted (IPW) analysis to correct for selection bias.

Results: Using standard analysis, males were significantly more likely to die before discharge and experience six other adverse outcomes. From IPW analysis, male sex causeda 60% increase in the odds of death before discharge (OR=1.60, 95% confidence interval: 1.18-1.94). Standard unweighted results were significantly biased towards increased risk of adverse outcomes for males (p=0.006) compared to IPW results for which three outcomes no longer significantly associated with male sex.

Conclusion: Standard statistical methods generally overestimate the casual effect of sex among VLBW infants.

Introduction

The “male disadvantage” for increased mortality and morbidity was first studied in 1933 [1] and was reported among premature infants by Naeye and colleagues [2] in 1971. Studying sex differences in outcomes among less developed infants is of interest due to their increased risk of mortality and morbidity. Some previous studies have observed males to have higher mortality only among infants with low gestational age (GA) or birth weight (BW), but differences were not seen among those with a higher GA or BW [3–5].

Among very low birth weight (VLBW) infants, defined as those with BW < 1500 g, the higher incidence of respiratory distress syndrome (RDS), pulmonary interstitial emphysema, anemia, low Apgar scores at five minutes, and other adverse outcomes in males was reported more than three decades years ago [6]. A systematic review [7] found strong evidence for increased mortality among premature and low birth weight males, with 26 (81%) of the 32 studies reviewed showing increased mortality for males, and the remaining 6 studies (19%) finding no gender difference in mortality. Other studies not included in the systematic review [7] have also found increased mortality among premature neonates, in addition to increased incidence of bronchopulmonary dysplasia (BPD), intraventricular hemorrhage (IVH), more neurological, pulmonary, cardiovascular and infectious morbidities, as well as a higher rate of combined adverse outcomes [8–14].

When studying VLBW infants, artificially truncating the distribution of all births at < 1500 g could induce a sample bias that affects estimates of sex differences in outcomes in this subpopulation because males with a higher BW at a given GA will be excluded. Males generally have a higher BW than females of the

same GA, particularly at earlier GAs. This can be seen by examining the mean GA for males and females by BW in the graph of all 38,607 births ≥ 22 weeks GA at the study institution (Fig. 1).

The directed acyclic graph (DAG) in Fig. 2A depicts the assumed causal relationship between sex, BW, GA, unmeasured covariates (e.g., maternal health status and lifestyle factors such as smoking and drug use) and infant outcomes in all births. Infant sex is causally related to outcomes and sex causally influences BW, which in turn influences GA (as discussed above), with both BW and GA influencing infant outcomes. VLBW infants are selected from all births by conditioning on BW (i.e., BW < 1500 g) as depicted in Fig. 2B. Examining Fig. 2B reveals that conditioning on BW blocks some of the causal influence of sex on outcomes that would have been mediated by BW and GA (since GA is causally influenced by BW). Using multivariable logistic regression analysis to adjust for BW and/or GA will yield biased estimates of sex differences in outcomes since BW and GA are casual mediators of the influence of infant sex. Adjusting for BW and GA would remove the causal effects of sex on outcomes that are mediated by these variables.

Selection bias due to conditioning on BW results in sex imbalances in GA, which is considered to be a form of confounding since males and females are not selected independently of GA in the VLBW subpopulation, and GA influences outcomes [15]. This selection bias renders estimation of the causal effect of sex on outcomes problematic in the VLBW population since GA is both a casual mediator and confounder. The purpose of this study is to estimate the causal effect of sex on outcomes in the neonatal intensive care unit (NICU) among VLBW infants.

Methods

This was a single center retrospective cohort study approved by the Baylor College of Medicine Institutional Review Board (IRB, protocol H-51590). This study was performed in accordance with the Declaration of Helsinki. Study data was obtained from, and all data definitions were governed by the Vermont Oxford Network (VON). No funding was provided to support this study. The dataset analyzed for during the current study is not publicly available due to IRB and VON policies that strictly protect the data as privileged and confidential, but the corresponding author will make every effort to accommodate reasonable requests for information about the study data. The study inclusion criteria were infants with BW < 1500 g who were admitted to the NICU on the main campus of a large tertiary children's hospital in the southwest United States from January 1, 2016 through December 31, 2020. The 187 bed NICU admits level II to IV infants from the hospital's high-risk delivery service as well as outborn infants for subspecialty service. Infants with major congenital anomalies (major birth defect, congenital heart disease, gastrointestinal defect, congenital diaphragmatic hernia or skeletal dysplasia), infants who died in the delivery room and infants with missing sex data were excluded from the study. Neonates with a gestational age less than 22 weeks or a birth weight below 500 g were excluded since they are not considered candidates for intensive care because they are too immature to survive [16]. Male sex was the exposure of interest and mortality before discharge was the primary outcome. The 25 secondary outcomes are listed and defined, where appropriate, in the Supplementary information.

The distributions of continuous variables were summarized with the mean ± standard deviation and compared for males versus female using the Wilcoxon rank sum test. The distributions of categorical variables were summarized with frequencies and percentages and compared for males versus female using Fisher's exact test. Inverse probability weighted (IPW) analysis was used to make unbiased comparisons of outcomes that differed significantly based on Fisher's exact test. IPW analysis is used for causal inference to adjust for confounding and selection bias by analyzing a pseudo-population in which the distributions of BW and GA are independent of sex, as if infant sex was randomized across these covariates [15]. To implement IPW analysis, first, the propensity score was computed for each patient from a logistic regression model with BW and GA used to predict male sex. (Here, propensity score represents the estimated probability of being male based on BW and GA.) Then, inverse probability weights were computed as the reciprocal of the propensity score. Next, the association of male sex with each outcome was estimated using GEE models fit with IPW data. Finally, for the sake of comparison, the same GEE models were fit to the original unweighted study data to show the effect of selection bias on standard estimates of the association of sex with each outcome. The paired t-test was to compare odds ratios across outcomes obtained from IPW vs unweighted analyses. Multivariable GEE models that included GA and BW in addition to sex as predictors of the primary outcome (death) were fit with both IPW and unweighted analysis to examine whether the true relationships of GA and BW were preserved in the IPW data compared to the original data. R version 4.3.0 (R Foundation for Statistical Computing, Vienna, Austria) was used for data analysis, with the geeglm function from the "geepack" library used to compute (IPW) estimates of the odds ratios with 95% confidence intervals derived from the robust variance estimator from generalized estimating equations (GEE) with an independent working correlation structure [15].

Results

There were 1339 VLBW admissions to the institution from January 1, 2016 through December 31, 2020, with 133 excluded due to congenital anomalies, 37 excluded due to death in the delivery room, and 4 excluded due to missing sex data. Of the remaining infants, another 30 with a birth weight less than 500 g were excluded leaving1135 infants meeting the study inclusion criteria, all of which were born with a gestational age of 22 weeks or greater. The final study analytic cohort included 592 (52.2%) males and 543 females (47.8%).

Baseline characteristics and adverse neonatal outcomes are compared for males versus females in Table 1. A significantly higher proportion of males died before discharge ($p = 0.004$), had RDS ($p = 0.024$), Apgar score < 7 at 5 minutes ($p < 0.001$), intubation during initial resuscitation ($p = 0.005$), hypothermia ($p = 0.005$), severe intraventricular hemorrhage (IVH, $p < 0.001$) and surfactant therapy ($p = 0.002$).

Table 1
Comparison of baseline characteristics and adverse outcomes for VLBW males versus females.

	Female (n = 543)	**Male (n = 592)**	**p-value**
Baseline Characteristics			
Birth weight (grams)[1]	1016.6 ± 279.5	1015.2 ± 281.2	0.957
Gestational Age (weeks)[1]	28.2 ± 2.8	27.8 ± 2.7	0.011*
Maternal Race[2]			
Black	175 (32.2)	197 (33.3)	0.752
White	328 (60.4)	351 (59.3)	0.716
Asian	38 (7.0)	41 (6.9)	1.000
Native American	1 (0.2)	3 (0.5)	0.626
Pacific Islander	1 (0.2)	0 (0)	0.478
Mother of Hispanic Ethnicity	180 (33.2)	191 (32.3)	0.752
Multiple Gestation[2]	159 (29.3)	203 (34.3)	0.074
Prenatal Care[2]	537 (98.9)	581 (98.1)	0.336
Antenatal Steroids[2]	487 (87.3)	515 (84.6)	0.202
Antenatal Mg Sufate[2]	398 (73.3)	429 (72.5)	0.789
Chroioamnionitis[2]	39 (7.0)	46 (7.6)	0.821
Maternal Hypertension[2]	205 (37.8)	210 (35.5)	0.459
Maternal Diabetes[2]	33 (6.1)	32 (5.4)	0.702
Vaginal Delivery [2]	101 (18.6)	135 (22.8)	0.092
Adverse Neonatal Outcomes			
Death before discharge[2]	47 (8.7)	84 (14.2)	0.004*
Late Onset Sepsis[2]	51 (9.4)	76 (12.8)	0.073
BPD – moderate to severe[2]	212 (39.0)	240 (40.5)	0.628
*Statistically significant difference ($p < 0.05$)			

	Female (n = 543)	Male (n = 592)	p-value
RDS[2]	341 (62.8)	410 (69.3)	0.024*
Pneumothorax[2]	25 (4.6)	43 (7.3)	0.061
Severe ROP[2]	31 (5.7)	33 (5.6)	1.000
ROP surgery[2]	11 (2.0)	10 (1.7)	0.826
Patent ductus arteriosus[2]	137 (25.2)	129 (21.8)	0.183
PDA surgery[2]	19 (3.5)	19 (3.2)	1.000
NEC[2]	31 (5.7)	40 (6.8)	0.540
NEC surgery[2]	36 (6.6)	57 (9.6)	0.083
Gastrointestinal perforation[2]	17 (3.1)	29 (4.9)	0.136
Surgical site infection[2]	4 (0.7)	3 (0.5)	0.716
Cystic Periventricular Leukomalacia[2]	11 (2.0)	15 (2.5)	0.692
Length of Stay (days)[2]	80.5 ± 55.8	81.4 ± 60.8	0.992
Apgar score < 7 at 5 minutes[2]	111 (20.4)	192 (32.4)	< 0.001*
Oxygen during initial resuscitation[2]	500 (92.1)	551 (93.1)	0.571
Face mask ventilation during initial resuscitation[2]	339 (62.4)	381 (64.4)	0.537
Intubation during initial resuscitation[2]	204 (37.6)	272 (46.0)	0.005*
Epinephrine during resuscitation[2]	10 (1.8)	13 (2.2)	0.834
Cardiac Compressions[2]	12 (2.2)	24 (4.1)	0.090
Nasal CPAP during initial resuscitation[2]	371 (68.3)	372 (62.8)	0.053
Hypothermia[2]	25 (4.6)	53 (9.0)	0.005*
Early Onset Sepsis[2]	9 (1.7)	11 (1.9)	0.826
Severe IVH[2]	37 (6.8)	79 (13.3)	< 0.001*
*Statistically significant difference (p < 0.05)			

	Female (n = 543)	Male (n = 592)	p-value
Surfactant therapy[2]	288 (53.0)	368 (62.2)	0.002*
*Statistically significant difference ($p < 0.05$)			

1. Mean ± standard deviation, Wilcoxon rank sum test p-value.
2. Frequency (%), Fisher's exact test p-value.

The seven adverse outcomes that males were significantly more likely to experience were analyzed in unweighted and IPW analyses (Table 2). Across the seven outcomes, the mean OR = 1.66 for the unweighted analysis compared to the mean OR = 1.50 for the IPW analysis, indicating significant bias towards increased risk of adverse outcomes for VLBW males in unweighted analysis results ($p = 0.006$). This discrepancy represents a [(0.66 − 0.50)/0.50]x100% = 32.0% average upward bias in the strength of the association above the null hypothesis for standard unweighted analyses. Three of the seven (42.9%) outcomes no longer differed significantly by sex in IPW analysis (RDS, intubation during initial resuscitation and surfactant therapy). All outcomes except severe IVH showed a bias towards increased odds for males. To demonstrate that associations with GA and BW were preserved in the IPW data, for the primary outcome of death, when GA was included in the regression model with sex, the adjusted odds ratio for GA (weeks) was 0.617 (95% CI: 0.512–0.722) in the IPW analysis compared to 0.613 (95% CI: 0.509–0.718) in the unweighted analysis. When BW was included in the regression model with sex to predict death, the adjusted odds ratio for BW (grams) was 0.996 (95% CI: 0.995–0.997) in both the IPW and BW analysis.

Table 2
Unweighted and IPW analyses of association of male sex with adverse outcomes males were more likely to experience.

Outcome	Unweighted OR (95% CI)	IPW OR (95% CI)
Death before discharge	1.75 (1.37–2.12)*	1.60 (1.18–1.94)*
RDS	1.33 (1.09–1.58)*	1.11 (0.86–1.36)
Apgar score < 7 at 5 minutes	1.87 (1.60–2.14)*	1.63 (1.36–1.90)*
Intubation during initial resuscitation	1.41 (1.18–1.65)*	1.19 (0.95 – 0.42)
Hypothermia	2.04 (1.55–2.53)*	1.99 (1.49–2.48)*
Severe IVH	1.75 (1.37–2.12)*	1.76 (1.36–2.17)*
Surfactant therapy	1.45 (1.22–1.69)*	1.21 (0.97–1.45)
*Indicates statistically significant association with infant sex (males are the “exposed” cohort)		

Discussion

In NICU outcomes that differed by sex (death before discharge, RDS, Apgar score < 7 at 5 minutes, intubation during initial resuscitation, hypothermia, severe IVH and surfactant therapy) this study found significantly higher estimated odds of adverse outcomes for males in unweighted analysis compared to IPW analysis. IPW analysis appropriately addresses confounding from BW and GA that occurs due to selection bias when artificially truncating the population of all births at birth weights less than 1500 grams to create the VLBW subpopulation. Thus, this finding reveals that studies using standard statistical methods to test for sex differences in VLBW infants are generally reporting estimates biased towards increased risk of adverse outcomes for males. The three outcomes (RDS, intubation during initial resuscitation and surfactant therapy) that became non-significant in IPW analysis results that remove the confounding effect of GA and BW due to selection bias are greatly influenced by underdevelopment of the lungs, with sex evidently playing less of a role.

The finding that VLBW males at the study institution were born at a significantly lower GA is consistent with previous research [9, 13, 17]. In this study, since sex was significantly associated with both death and GA, and GA was significantly associated with death after controlling for GA, GA would be considered a significant mediator or confounder of the relationship of sex with mortality as defined by causal steps analysis [18]. Although statistics cannot disentangle confounding from causally mediated effects [19], the results of this study provide evidence that GA is a confounder due to selection bias in the VLBW subpopulation. That fact that GA is also a causal mediator of sex differences in outcomes can be ascertained based on clinical knowledge. Among all births, many studies [11, 20–30] have found males to be born at a lower GA than females, with a hypothesized reason being that male fetuses are on average heavier than females of the same GA [21, 22]. That fact that lower GA is casually related to death and other adverse outcomes is evident beyond question. Therefore, GA is both a confounder and a casual mediator of sex differences in mortality and other adverse outcomes.

The results of the present study provide unbiased estimates of the casual effect of sex on mortality and other adverse outcomes in the NICU among VLBW infants. Although much remains unknown about the reason for these sex differences, hormones, genetics, immunology, physiology, microvascular function and growth factors have been proposed to play roles in the male disadvantage in outcomes among underdeveloped infants [12, 31, 32]. Research suggests male fetuses biologically prioritize growth pathways in order to facilitate an evolutionary advantage later in the reproductive stage of life, which renders males less adaptable in utero, thereby increasing the risk for perinatal morbidity and mortality compared to female fetuses that prioritize reserve capacity and adaptability [33]. Sex differences in placental development and function have been hypothesized to be a reason for increased risk of pregnancy complications for male fetuses [34].

Accurate estimation of sex differences in outcomes will facilitate investigation of the biological mechanisms involved so that targeted interventions can be developed to mitigate the male disadvantage. Some research has shown the sex gap in mortality among very preterm infants to be narrowing over time, resulting in speculation that males may preferentially benefit from new treatments such as antenatal steroids and surfactant [14, 35–37]. Studies in both animals [38–40] and humans [10, 41–43] have found differential treatment responses among fetal and neonatal males compared to females. There is even evidence that preterm males' neonatal responses to maternal nutrition differs from that of females, and maternal breastmilk composition varies by infant sex [44]. Therefore, sex-specific strategies need to be investigated in order identify treatments that are best suited for an individual infant. This is not a new idea. In 2005 the Food and Drug Administration published recommendations [45] for research into sex differences in treatment responses and in 2014 the National Institute of Health created requirements [46] for biomedical research grant applications involving preclinical studies to include examination of sex as a variable. Despite these past recommendations, greater emphasis on research specifically investigating sex differences in treatment responses is still needed today.

This study was conducted at a single institution with a unique NICU patient population, so the findings might not generalize to other NICUs. This study is also limited by the retrospective observational study design since statistics cannot discriminate causal mediation from confounding with an observational study. However, since sex cannot be randomized as an intervention, the IPW analysis used in this study provides a valid method to estimate the causal effect of sex on NICU outcomes in the VLBW population.

This is the first published study to show that standard statistical methods that have been used in previous research yield biased estimates of sex differences in outcomes among VLBW infants. This study provides valid estimates of the casual effect of sex on mortality and other adverse NICU outcomes among VLBW infants. Accurate estimates are necessary to help us understand the causal pathways leading to sex differences in NICU outcomes. This knowledge will support development of targeted interventions that take infant sex into account.

Declarations

Conflict of Interest: The author has no competing financial interests related to this study.

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Author contributions: The study wasconceived of and conducted solely by JH.

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Figures

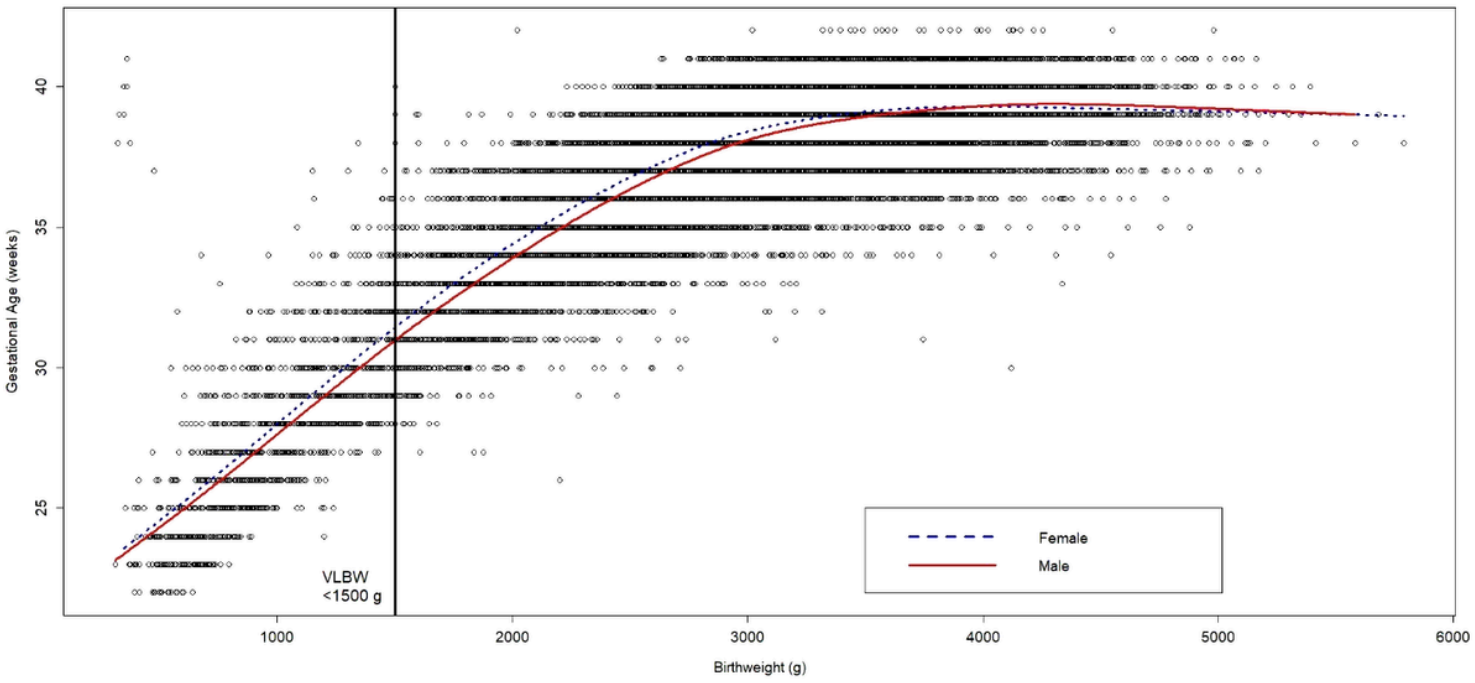

Figure 1

Scatterplot of all 38,607 births ≥ 22 weeks GA at the study institution with lines indicating the mean GA for males and females by BW.

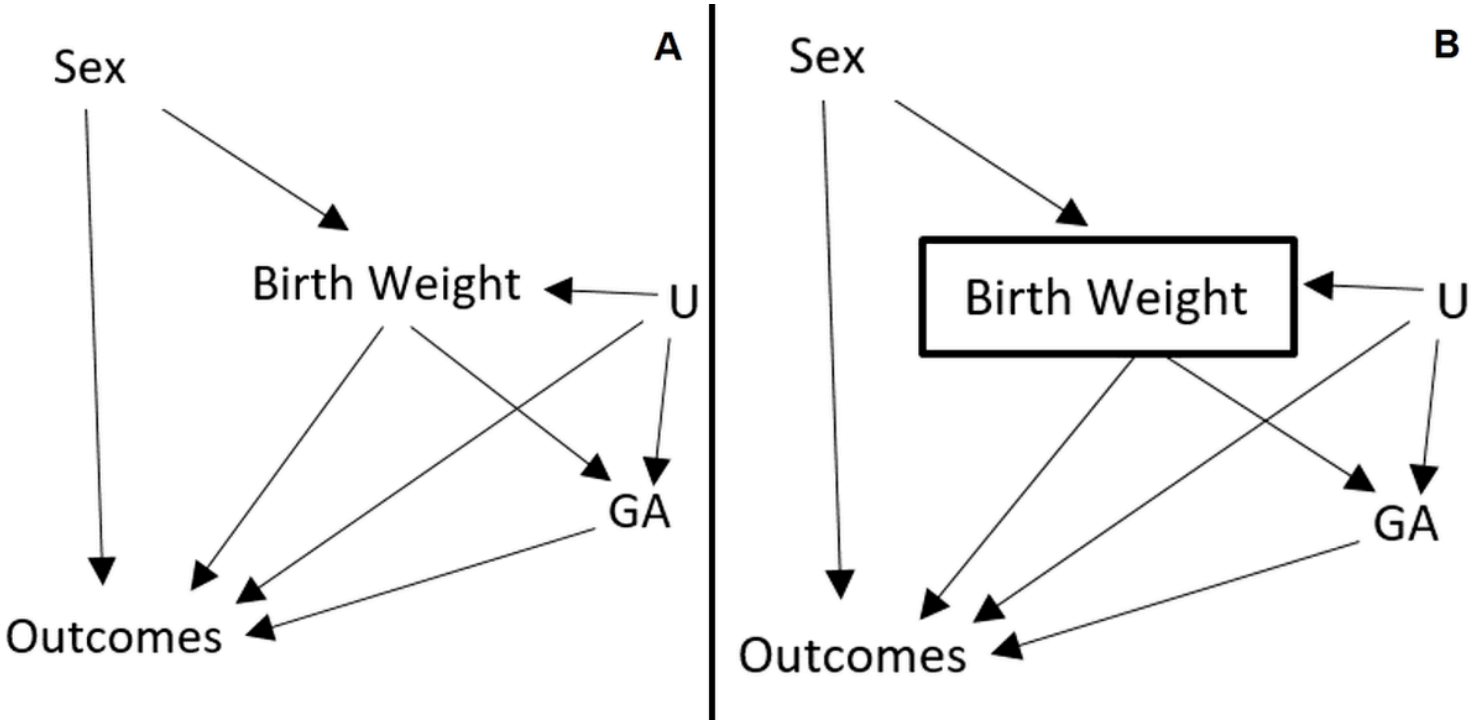

Figure 2

DAGs with U representing a vector of unmeasured covariates (e.g., maternal smoking status and drug use) for A) all births and B) VLBW infants, with box around BW indicating conditioning on BW < 1500 g.