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Heightened risk of preterm birth and growth restriction after a first-born son

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ABSTRACT

Purpose: In Scandinavia, delivery of a first-born son elevates the risk of preterm delivery and intrauterine growth restriction of the next-born infant. External validity of these results remains unclear. We test this hypothesis for preterm delivery and growth restriction using the linked California birth cohort file. We examined the hypothesis separately by race and/or ethnicity.
Methods: We retrieved data on 2,852,976 births to 1,426,488 mothers with at least two live births. Our within-mother tests applied Cox proportional hazards (preterm delivery, defined as less than 37 weeks gestation) and linear regression models (birth weight for gestational age percentiles).
Results: For non-Hispanic whites, Hispanics, Asians, and American Indian and/or Alaska Natives, analyses indicate heightened risk of preterm delivery and growth restriction after a first-born male. The race-specific hazard ratios for preterm delivery range from 1.07 to 1.18. Regression coefficients for birth weight for gestational age percentile range from −0.73 to −1.49. The 95% confidence intervals for all these estimates do not contain the null. By contrast, we could not reject the null for non-Hispanic black mothers.
Conclusions: Whereas California findings generally support those from Scandinavia, the null results among non-Hispanic black mothers suggest that we do not detect adverse outcomes after a first-born male in all racial and/or ethnic groups.

Introduction

The delivery of a live infant at less than 37 completed weeks (i.e., preterm) elevates the risk of infant mortality by 25-fold [1]. In addition, children born preterm—especially those born at very early gestational ages (i.e., less than 32 weeks)—show elevated respiratory distress and asthma, impaired cognitive development, school difficulty, hyperactivity, lower educational attainment, and lower adult earnings [2–4]. The incidence of preterm birth in the United States (12 per 100 live births) has remained relatively stable over time and ranks among the top five of all 75 high-income countries [5,6].

Research using Scandinavian registry data finds that delivery of a first-born child that is male elevates the risk of preterm delivery of the next-born infant [7,8]. This elevated risk occurs regardless of preterm status of the first born and regardless of sex of the second born infant. Given that a first-born male precedes adverse clinical symptoms in the subsequent birth, we view a first-born male as potentially harmful for the second birth [9].

Reasons for the discovered association between a first-born male and adversity in the subsequent pregnancy invoke two general mechanisms. The first involves maternal immunologic priming against specific alloantigens produced by the male fetus. Whereas the mother's first exposure to these antigens may not induce an inflammatory reaction, researchers posit that they may elicit an inflammatory cytokine cascade in the subsequent pregnancy, which may in turn accelerate the timing of parturition, affect fetal growth, or increase the risk of fetal demise [10,11]. A second report, based on results from 18th and 19th century Finland, contends that males more than females exert a higher cost to the mother in terms of her reduced lifespan and her lower fitness of subsequent offspring [12,13]. This heightened maternal load of rearing males may elicit responses that, in turn, elevate the risk of adverse outcomes for the subsequent pregnancy.

Further examination of these two general descriptions, and potentially other hypotheses, would seem warranted if these findings applied to populations outside Scandinavia. The United States

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contains a much more racial or ethnically diverse population of gravid mothers than that of Scandinavia. Such diversity includes potentially important sociocultural and biological differences that may increase or decrease the risk of preterm delivery. This diversity across races and/or ethnicities suggests potential effect measure modification of the first-born male and/or preterm association. Recent analyses, for example, show different prevalence of genetic polymorphisms and innate immune system markers for non-Hispanic black, non-Hispanic white, and Hispanic gravid women [5,14,15]. These differences may lead to different immune responses, across these groups, after a male birth. Non-Hispanic black mothers, moreover, show the highest incidence of preterm (i.e., 16.3 per 100 births) of any race and/or ethnicity in the United States. [16]. This heightened incidence, of which a substantial fraction remains unexplained after accounting for established risk factors, suggests potentially distinct etiologies for this race and/or ethnicity [17].

We set out to replicate the finding that a first-born male precedes an increased risk of preterm or growth restriction in the subsequent birth. This analysis uses a unique data set in California on over 1.4 million consecutive sibling pairs. Given the racial and/or ethnic diversity of California, we examine whether the association differs by race and/or ethnicity. In Scandinavia, a first-born male increases not only the risk of preterm but also growth restriction [7,8]. Researchers report reduced birth weight among both male and female births after a first-born male [8]. This association with birth weight remains after accounting for the independent association with earlier parturition. We, therefore, also examine intrauterine growth restriction.

Methods

Data and variables

We retrieved birth records from the California linked Birth Cohort Files (1991–2010). The time span for which we retrieved data reflects the longest series of linked data available to us at the time of the test. These files merge birth and fetal and infant death certificates for all births in California with Office of Statewide Health and Planning maternal and infant hospital discharge data from pregnancy, at delivery, and up to one year after delivery, as described previously [18,19]. The data sets link multiple births to the same woman and contain maternal and pregnancy characteristics found on the birth certificate and clinical detail from the delivery hospitalization for 96.6% of all inpatient live births.

We restricted the sample to mothers with first- and second-born singleton live births over the study period. We restricted to first-born children starting in 1991 and required that parity = 0 and birth order = 1. To ensure correct identification of consecutive births to the same mother, we required that the maternal birth date match across records and that the month and year of the preceding birth listed on the second birth certificate matched the month and year of birth recorded on the first birth certificate. The file included over 11 million live births. Of these births, 2,399,585 mothers had two or more records, and 1,609,135 gave birth to their first and second singleton live-born infant. The fraction of births that qualified for study inclusion appears consistent with expectations based on parity-specific fertility tables [20].

We based gestational age on the date of the last menstrual period. We sequentially removed 11 mothers who gave birth to an infant of undetermined sex, 156,942 mothers who had a pregnancy of unknown gestational length, gestational age (GA) shorter than 20 weeks, or GA longer than 44 weeks, 10,144 mothers with newborns that had implausible birth weight for GA [21], 14,117 mothers of unknown race and/or ethnicity, and 1,433 mothers who had an interpregnancy interval less than 36 days (i.e., <36 days between delivery of first live birth and estimated date of conception of the second-live birth, which the literature reports as implausible) [22]. This process left us with a sample of 2,852,976 births to 1,426,488 mothers for the analysis.

We used birth weight percentile as a measure of intrauterine growth, which captures size for the infant's particular GA at birth. We used standardized, sex-specific birth weight for gestational age tables to assign birth weight percentiles [23]. These percentiles improve on the categorical appropriateness-for-gestational age metric; in that, they capture a nearly continuous measure of growth per GA level. We also preferred this metric over low birth weight (i.e., less than 2500g) because low birth weight may arise from early delivery, restricted growth, or both. We retrieved all analytic variables from the birth certificate save one: indication of spontaneous preterm delivery. We retrieved this variable using diagnostic and procedure codes from hospital discharge records.

Analysis

Preterm birth

Our analytic strategy controls for confounding by generally time-invariant maternal factors (e.g., socioeconomic status, genetics), the propensity to deliver males, and fertility decisions based on characteristics of the first birth. Earlier studies from Scandinavia use a design that we deem as most suitable to testing our hypothesis. To permit comparison of our results with those from Scandinavia, we therefore structured analyses similarly [7]. We defined preterm delivery as a live birth at less than 37 weeks of gestation. We applied a Cox proportional hazards model with gestational age (in weeks) as the time axis and censored all observations at 37 weeks. We also assessed departure from proportional hazards but found none for any race and/or ethnicity. For this reason, we report the "average" generated hazard ratios (HR) and 95% confidence intervals (CIs) for the preterm analysis.

Comparison of birth outcomes across sibling pairs controls for time-invariant maternal factors that cause preterm birth. For this reason, we included only a limited set of variables to control for confounding: maternal age at second birth, interpregnancy interval (in months), and sex of the second-born infant. We examined separately each of the following racial/ethnic groups: non-Hispanic white, non-Hispanic black, Hispanic, non-Hispanic Asian and/or Pacific Islander, and American Indian and/or Alaskan Native. Given the confounding induced by adjusting for preterm status of the first child (see directed acyclic graph analysis [Fig 2] in Mortensen et al. [7]), we did not control for this variable.

We then performed four sensitivity analyses to examine the robustness of findings. First, we repeated the general analysis using only values with ultrasound dating for GA (available only for 2007–2010; n = 104,764) [24]. Second, we assessed whether selection into a second live birth accounted for the results. If the likelihood of having a second child depends on the sex and/or preterm birth status of the first born, this selective fecundity may induce bias. We therefore used all first-born infants in the birth cohort files (including mothers who stopped at one birth) to derive propensity score weights of having a second infant, conditional on each of the four sex and preterm combinations. We also controlled for race and/or ethnicity, maternal education status, and maternal age when deriving these propensity scores. We used the inverse probability of these propensity scores as weights and repeated the analysis. Third, we assessed the likelihood of unmeasured confounding by a shared factor across both pregnancies (as diagrammed previously) [7] by examining whether preterm status of the first born predicts infant sex of the second born, and whether sex of the first born predicts sex of the second born. Fourth, we restricted the analyses to only spontaneous preterm deliveries (i.e., those preceded by spontaneous