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Heightened Risk of Preterm Birth and Growth Restriction following 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/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 <37 weeks gestation) and linear regression models (birthweight for gestational age percentiles).

RESULTS: For non-Hispanic whites, Hispanics, Asians, and American Indian / Alaska Natives, analyses indicate heightened risk of preterm delivery and growth restriction following a first-born male. The race-specific hazard ratios for preterm delivery range from 1.07 to 1.18. Regression coefficients for birthweight-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.

CONCLUSION: Whereas California findings generally support those from Scandinavia, the null results among non-Hispanic black mothers suggest that we do not detect adverse outcomes following a first-born male in all racial/ethnic groups.

MeSH headings: first-born, birth order, male, sibling, preterm, growth restriction

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., <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 immunological 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 of Scandinavia. The United States contains a much more racial/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 race/ethnicities suggests potential effect measure modification of the first-born male / 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 (14, 5). These differences may lead to different immune responses, across these groups, following a male birth. Non-Hispanic black mothers, moreover, show the highest incidence of preterm (i.e., 16.3 per 100 births) of any race/ethnicity in the U.S. (16). This heightened incidence, of which a substantial fraction remains unexplained after accounting for established risk factors, suggests potentially distinct etiologies for this race/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 employs a unique dataset in California on over 1.4 million consecutive sibling pairs. Given the racial/ethnic diversity of California, we examine whether the association differs by

race/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 following 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 datasets 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/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 upon 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., <2,500gm) since low birthweight 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/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 / Pacific Islander, and American Indian / Alaskan Native. Given the confounding induced by adjusting for preterm status of the first child (see directed acyclic graph analysis [Fig 2] in Mortensen and colleagues (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/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 onset of labor or premature rupture of membranes) as the ”time-to-delivery” dependent variable to rule out the possibility that iatrogenic, clinically-indicated preterm deliveries drove results.

Birth Weight Percentile

We specified an ordinary-least squares linear regression model with birth weight percentile as the dependent variable and controlled for all confounders specified in the preterm birth analyses. We examined each racial/ethnic group separately. In addition,

we performed sensitivity analyses analogous to those described for analyses of preterm birth. For the approach that examines the potential role of selective fecundity (i.e., the inverse-weighted propensity score analysis), we created propensity score weights of having a second infant, conditional on each of the four sex- and small for gestational age- combinations. We defined small-for-gestational age (SGA) in a dichotomous fashion, using the conventional cutpoint of less than or equal to the tenth percentile of birthweight for gestational age (25).

Both the Stanford University Institutional Review Board and the California State Committee for the Protection of Human Subjects approved this study.

RESULTS

Infants born to non-Hispanic white mothers account for the majority (43.4%) of births, followed by Hispanic (35.2%), Asian (14.9%), and non-Hispanic black (6.0%) births. Infants born to non-Hispanic black mothers show the greatest incidence of preterm delivery (11.4%) of any race/ethnicity and infants born to non-Hispanic whites the lowest (6.3%). The percent of second births delivered preterm after a first-born son slightly exceeds the percent of preterm deliveries after first-born daughters (7.9 vs. 7.3 percent across all race/ethnicity and sex strata). Second births following a first-born son also have lower mean birthweight across all race/ethnicities than do second births following a first-born daughter (weighted mean difference across all race/ethnicity and sex strata = 23.4 grams). Table 1 further describes the characteristics of second-born infants by race/ethnicity.

For non-Hispanic whites, Hispanics, and Asians, adjusted hazard ratios (HRs) for

preterm delivery (for second-born infants given that the first-borns were males) range from 1.07 to 1.10 and the 95% confidence intervals (CIs) do not contain the null value (Table 2). American Indian/Alaska native (AI/AN) infants show the greatest hazard ratio, although the confidence interval is much wider owing to fewer observations (HR = 1.18, 95% CI: 1.00—1.40). By contrast, among non-Hispanic blacks we observe no association (HR = 1.00, 95% CI: 0.96—1.04).

For non-Hispanic whites, Hispanics, and Asians, birthweight for GA of the second birth is 0.7 to 1.13 percentile points lower after a first-born male; CIs for these estimates exclude the null value (Table 2). The highest intrauterine growth deficit occurs among AI/AN infants (coef. = -1.49, 95% CI: -2.9— -0.08). By contrast, growth results for non-Hispanic blacks do not provide evidence to reject the null hypothesis (coef. = -0.30, 95% CI: =0.68 – 0.09). To assist with interpreting clinical relevance of these growth results, we used the conventional 10^{th} percentile cutpoint to define SGA and performed logistic regression analyses. Results show a range of between seven (non-Hispanic white) to sixteen percent (AI/AN) increased odds of SGA following a first-born son. As with the original analyses, the result for non-Hispanic blacks cannot reject the null.

Sensitivity Analyses

To assess the role of GA measurement on our results, we repeated the analyses using only values with ultrasound dating. The general pattern of results remained the same (Supplemental Tables 1 and 2), although results were imprecisely estimated for smaller samples (e.g., American Indian/Alaskan Native). Next, to determine whether selective fecundity decisions drove results, we repeated preterm analyses using the

inverse propensity score weights of having a second infant, conditional on each of the four sex- and preterm- combinations of the first-born child. Weighted analyses yielded essentially the same inference as the results shown in Table 2 (Supplemental Table 3).

To address the issue of pregnancy losses occurring between two live births, we removed from the analysis any mother with fetal death between these live births. This process ensures that the births we analyze represent consecutive live birth records of birth order 1 and 2. Results appear substantially similar to those shown in Table 2 in that we observe an increased risk of preterm for all race/ethnicities save for blacks (available upon request).

We examined whether preterm status, or sex, of the first-born predicted infant sex of the second-born. Results did not provide evidence that preterm status of the first-born or sex of the first-born were associated with sex of the second-born (results available upon request). Unmeasured confounding by these first-pregnancy factors do not appear to drive our main findings. Next, we examined whether the risk of preterm delivery following a first-born male varies by sex of the second-born. Results indicate effect modification by sex of the second-born (HR for second-born males = 1.09, 95% CI: 1.07—1.11; HR for second-born females = 1.06, 95% CI: 1.05—1.08; χ^2 for interaction term = 3.2, $p = .07$), although the magnitude of effect modification is small, especially given the large sample of births. We then restricted analyses to spontaneous preterm deliveries. Table 3 shows that point estimates for all race-specific HRs move further away from the null hypothesis relative to the original tests. Statistical inference, however, does not change.

DISCUSSION

We set out to replicate findings from Scandinavia that a first-born male increases the risk of preterm among the second live birth (7). Using a large, ethnically diverse birth registry that links sequential births by mother, we find support for the hypothesis in almost all race/ethnicities. For births to non-Hispanic white, Hispanic, and Asian mothers, the hazard of preterm delivery for a second birth increases between seven to ten percent after a first-born son. By contrast, results for infants born to non-Hispanic black mothers do not show an elevated hazard of preterm delivery for the second birth. The magnitude and statistical inference for intrauterine growth results follow the same pattern as the preterm results. Whereas findings generally support those from Scandinavia, the null results among non-Hispanic black mothers suggest that the burden of a first-born son to a subsequent pregnancy does not appear universal.

Strengths of our study include information on all consecutive first and second births to California mothers over a twenty year period. The large and diverse study population, moreover, provides strong statistical power to detect modest associations. The linked nature of births by mother also permits a within-mother analysis that controls for confounding by factors that tend to remain stable across consecutive pregnancies (e.g., genetics, socioeconomic status). The consistency of findings across two separate outcomes, and to several sensitivity analyses, further supports the hypothesis.

Limitations include that we observed only live birth outcomes and could not measure other indicators of fertility (e.g., time to pregnancy, hormonal profiles). We, moreover, classified births by race/ethnicity given that self-identified race/ethnicity predicts preterm birth independently of socioeconomic and medical variables (26).

These categories, however, may obscure important heterogeneity in risk. Measurement error in gestational age estimation also remains an important issue especially in studies such as ours that examine births before routine ultrasound dating (24) . Although sensitivity analyses indicate that such measurement error does not account for our discovered findings in most race/ethnicities (Supplemental Tables 1 and 2), we acknowledge that studies focusing on ultrasound dated pregnancies may yield different coefficient estimates than our main results.

One mechanism that may account for the findings is that a male fetus, compared to a female fetus, invokes maternal immune hyperreactivity to fetally-encoded alloantigens (e.g., H-Y antigen complex encoded by the Y chromosome)(27). Although a maternal immune response to H-Y alloantigens commonly develops during pregnancy (28), if such a response is overly robust it might trigger a more generalized decrease in the tolerance of the mother to other paternally-derived major alloantigens (29, 30), and minor histocompatibility antigens (31). Development of increased maternal anti-fetal immune responses is plausible given that researchers commonly identify ”epitope spreading” in the evolution of many immune-mediated diseases (32). A spreading of anti-fetal reactivity to involve non-HY-encoded alloantigens would provide an explanation for the observation that both females and males appear at elevated risk of adverse outcomes following a first-born son. In addition to the HY antigen-disparity, pregnancy with a male fetus compared to a female fetus results in a more pro-inflammatory cytokine milieu (33, 34). Additional studies evaluating maternal anti-fetal alloreactivity during first and second pregnancies, and its relation with cytokine milieu of the placental-fetal unit, would assist with testing the importance of these potential

mechanisms.

Whereas historical life history research finds that males exert a higher reproductive cost to the mother than do females (12, 13), it remains unclear whether this finding holds in contemporary populations. Sons have greater average birth weight and height (35, 36). Sons also require more energy during gestation and lactation than do daughters (37, 38). The California birth file, however, does not include full information on these variables. In addition, mechanisms connecting this putative heightened energetic cost to preterm delivery of the second-born remain elusive. We anticipate that smaller clinical datasets which prospectively follow women and their children through pregnancy and post-partum may allow for more careful examination in the future of son/daughter differences in maternal costs.

Prior research documents that changing paternity attenuates the relation between a first-born male and subsequent growth restriction (8). These findings, which require replication, support that a first born son adversely affects the growth of subsequent pregnancies by enhancing specific maternal priming of reactivity against paternally-derived alloantigens. Such maternal anti-fetal immune reactivity would not be shared with paternally-derived alloantigens from a different father. However, we could not examine change in paternity from the first to second pregnancy, as the linked birth cohort file does not contain information on paternity. To the extent that mothers have two children with different paternity in the US more or less frequently than do mothers in Scandinavia, we caution against making cross-national comparisons of our birthweight-for-GA coefficients.

Whereas non-Hispanic black mothers show the greatest incidence of preterm

delivery, all race/ethnicities we analyzed save for blacks converge with previous findings. We offer one explanation *post hoc*. The anomaly may arise from the fact that a first-born male serves as a weak competing cause relative to the myriad other causes that may concentrate among non-Hispanic black mothers. To illustrate this point, we calculate a population attributable fraction of 6.7% of preterm births that statistically arise due to a first-born male. This population attributable fraction is relatively small, interpretational caveats notwithstanding (see (39)). Given the high background rate among non-Hispanic black mothers that arises from the complex interplay of social, economic, and biological factors (26), the slight increased risk of preterm birth or growth restriction following a first-born male may not elicit pathology.

Our replication of Scandinavian findings in an ethnically diverse setting largely supports that a first-born male heightens the risk of preterm delivery and growth restriction of the subsequent live birth. We view our work as contributing to the basic understanding of the etiology of preterm birth and growth restriction. Our work also may inform theories concerned with conservation of mechanisms in which male births trigger adversity in subsequent pregnancies. This adversity manifests not only in the outcomes we studied, but also in stillbirths (9). Furthermore, results should encourage pursuit of attendant hypotheses regarding the immunological basis of adverse outcomes following a first-born male.

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Table 1. Descriptive characteristics of second-born infants in California in relation to the sex of the mother's first-born infant, 1991-2010.

	N	Percent Preterm	Birthweight Percentile (SD)[1]	N	Percent Preterm	Birthweight Percentile (SD)[1]
First-born is male				**First-born is female**		
Second born is male						
All races/ethnicities	374,681	8.42	52.7 (28.2)	355,745	7.78	53.8
Non-Hispanic White	163,841	6.97	57.2 (27.6)	153,535	6.50	58.2 (27.4)
Non-Hispanic Black	22,028	11.75	45.2 (28.5)	21,227	11.69	45.5 (28.5)
Asian/Pacific Islander	56,026	9.00	44.4 (27.3)	53,964	8.13	45.4 (27.3)
Hispanic	131,071	9.42	52.0 (28.1)	125,462	8.52	53.4 (28.0)
American Indian /Alaskan Native	1,715	9.62	55.7 (29.2)	1,557	8.41	57.1 (28.7)
Second born is female						
All race/ethnicities	359,108	7.27	52.9 (28.1)	336,954	6.86	53.6 (28.2)
Non-Hispanic White	156,586	6.01	56.7 (27.6)	145,200	5.65	57.5 (27.6)
Non-Hispanic Black	21,385	11.12	45.4 (28.6)	20,639	11.12	45.5 (28.8)
Asian/Pacific Islander	53,165	7.46	45.4 (27.3)	50,020	6.94	45.7 (27.3)
Hispanic	126,376	8.08	52.5 (28.1)	119,493	7.55	53.4 (28.0)
American Indian /Alaskan Native	1,596	8.96	55.0 (29.3)	1,602	7.37	56.6 (28.6)

[1]removed 313 mothers who birthed <22 weeks gestation for whom birthweight for gestational age reference tables do not supply gender specific continuous birthweight for gestation percentile (n=1,426,175).

Table 2. Racial/ethnic-specific hazard ratios of preterm birth for the second born if first born was male, California 1991-2010. Referent group is first-born female. Each row represents a separate racial/ethnic specific test.*

	N	HR	Lower CI	Upper CI
Non-Hispanic White	619,162	1.07	1.05	1.09
Non-Hispanic Black	85,279	1.00	0.96	1.04
Asian/Pacific Islander	213,175	1.10	1.06	1.13
Hispanic	502,402	1.09	1.07	1.12
American Indian/Alaskan Native	6,470	1.18	1.00	1.40

* Each model adjusted for sex of second birth, maternal age at second birth, and interpregnancy interval (coefficients available upon request).

Table 3. Regression coefficients for birthweight for gestational age percentile of second born if first born was male, California births 1991-2010. Referent group is first-born female. Each row represents a separate racial/ethnic-specific test.*

	N	Coef.	Lower CI	Upper CI
Non-Hispanic White	619,076	-0.95	-1.08	-0.81
Non-Hispanic Black	85,223	-0.30	-0.68	0.09
Asian/Pacific Islander	213,123	-0.73	-0.96	-0.50
Hispanic	502,285	-1.13	-1.29	-0.98
American Indian/Alaskan Native	6,468	-1.49	-2.90	-0.08

* Each model adjusted for sex of second birth, maternal age at second birth, and interpregnancy interval (coefficient results for covariates available upon request). Percentiles of birthweight are sex and gestational week specific, from ref. 23.

Table 4. Sensitivity analysis. Hazard ratio (95% CI) of **spontaneous** preterm birth for the second born if first born was male, California 1991-2010. Referent group is first-born female. Each row represents a separate racial/ethnic-specific test.*

	HR	Lower CI	Upper CI
Non-Hispanic White	1.10	1.07	1.14
Non-Hispanic Black	0.97	0.91	1.02
Asian/Pacific Islander	1.13	1.08	1.18
Hispanic	1.14	1.11	1.18
American Indian/Alaskan Native	1.22	0.94	1.58

* Each race-specific model adjusted for sex of second birth, maternal age at second birth, and interpregnancy interval (coefficients available upon request). For sensitivity analysis, number of spontaneous preterm cases per race/ethnicity are as follows: non-Hispanic white = 19,367; non-Hispanic black = 4,672; Hispanic = 17,798; Asian / Pacific Islander = 8,339, American Indian / Alaskan Native= 237.