Research article

Population-based estimate of sibling risk for preterm birth, preterm premature rupture of membranes, placental abruption and pre-eclampsia

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Abstract

Background: Adverse pregnancy outcomes, such as preterm birth, preeclampsia and placental abruption, are common, with acute and long-term complications for both the mother and infant. Etiologies underlying such adverse outcomes are not well understood. As maternal and fetal genetic factors may influence these outcomes, we estimated the magnitude of familial aggregation as one index of possible heritable contributions.

Using the Missouri Department of Health's maternally-linked birth certificate database, we performed a retrospective population-based cohort study of births (1989–1997), designating an individual born from an affected pregnancy as the proband for each outcome studied. We estimated the increased risk to siblings compared to the population risk, using the sibling risk ratio, λ_s, and sibling-sibling odds ratio (sib-sib OR), for the adverse pregnancy outcomes of preterm birth, preterm premature rupture of membranes (PPROM), placental abruption, and pre-eclampsia.

Results: Risk to siblings of an affected individual was elevated above the population prevalence of a given disorder, as indicated by λ_s (λ_s (95% CI): 4.3 (4.0–4.6), 8.2 (6.5–9.9), 4.0 (2.6–5.3), and 4.5 (4.4–4.8), for preterm birth, PPROM, placental abruption, and pre-eclampsia, respectively). Risk to siblings of an affected individual was similarly elevated above that of siblings of unaffected individuals, as indicated by the sib-sib OR (sib-sib OR adjusted for known risk factors (95% CI): 4.2 (3.9–4.5), 9.6 (7.6–12.2), 3.8 (2.6–5.5), 8.1 (7.5–8.8) for preterm birth, PPROM, placental abruption, and pre-eclampsia, respectively).

Conclusion: These results suggest that the adverse pregnancy outcomes of preterm birth, PPROM, placental abruption, and pre-eclampsia aggregate in families, which may be explained in part by genetics.

Background

In the United States, 12.7% of births occur preterm (< 37 weeks) [1], approximately one-fourth of which occur due to preterm premature rupture of membranes (PPROM) [2]. Pre-eclampsia and placental abruption affect approximately 7% [3] and 1% [4] of all pregnancies, respectively. While many pregnancies share more than one of these complications, together they affect a significant portion of pregnancies and represent the most common reasons for early delivery. Moreover, adverse pregnancy outcomes are important causes of perinatal morbidity and mortality. For example, placental abruption, while uncommon, accounts for 12% of all perinatal deaths [5]. The incidence of preterm birth [1] and placental abruption [5] have increased over recent decades, further motivating additional study to understand susceptibility factors which contribute to these outcomes.

Prediction and prevention of these adverse outcomes is difficult. Etiologies underlying preterm birth, PPROM, placental abruption and pre-eclampsia are not well understood. Genetic studies are one way in which we can attempt to better understand these disorders. Such studies may identify genetic markers that can predict one's risk for a particular pregnancy outcome. Genetic studies may also identify novel proteins and/or pathways involved in the disorder.

Both maternal and fetal genetic factors may influence adverse pregnancy outcomes. Evidence suggests that maternal genetic factors contribute to preterm birth [6,7], PPROM [7-9], placental abruption [10,11] and pre-eclampsia [12-15]. In contrast, fetal effects on these outcomes have not been well studied. Several lines of evidence suggest that fetal genetic effects may influence adverse pregnancy outcomes. First, fetal genes that are paternally imprinted mainly control placental and fetal membrane growth [5]. Because the placenta and fetal membranes likely play a role in adverse pregnancy outcomes, fetal genes controlling these tissues may also contribute. Additionally, heritability studies, which estimate the relative portion of population variation in a trait due to genetics, suggest that preterm birth [16] and pre-eclampsia [17] are influenced in part by fetal genetic factors. Lastly, several studies suggest that paternity affects risk for preterm birth and pre-eclampsia. For example, several studies indicate that partner changes between pregnancies reduce risk of preterm birth [18,19] and pre-eclampsia [17,20-22]. Changes in paternity may reflect association with long interpregnancy intervals rather than paternity effects *per se*; however, for pre-eclampsia [14,23], fathers' family history affects risk for the disorder in their partners' pregnancies. For preterm birth, father's family history has been shown to have only a weak association with risk. While an early study of a Norway birth registry demonstrated a correlation between father and children's gestational ages [24], a more recent and extensive study of this registry suggested fathers contributed little to no risk to preterm delivery risk [25]. Also, paternal race has been associated with preterm birth risk [26,27]. Together, this data suggests that paternal genes expressed in the fetus may contribute to these disorders, motivating study of maternal-fetal influences, assessed by defining the infant as the proband, in addition to influences that are maternal-specific.

While multiple lines of evidence suggest the importance of genetic contributors in adverse pregnancy outcomes, observing clustering of such outcomes in families is necessary to assert genetic influences on a disorder. A disorder that does not aggregate in families is unlikely to be influenced by inherited factors. Hence, detecting an increased risk for a disorder among siblings or other family members of an individual born from a pregnancy affected by the same adverse outcome would further support genetic influences on these conditions. However, familial aggregation is not sufficient to claim genetic influences on a disorder. Since family members share both genes and environment, any similarities seen in families may be explained by genetic or shared environmental factors (such as in utero maternal environment) or by their interaction.

Two standard measures of familial aggregation are increase in risk to siblings of affected individuals, compared to the population risk for the disorder, the sibling risk ratio, λ_s[28], and compared to siblings of unaffected individuals, the sibling-sibling odds ratio (sib-sib OR) [29]. These measures have been estimated for a variety of disorders, ranging from single locus Mendelian disorders, such as cystic fibrosis [30], to complex disorders, including hypertension [31], type 2 diabetes [32], and myopia [33,34]. These familial aggregation measures have been incompletely documented in pregnancy outcomes. When considering mother as the affected individual, investigators have reported increased risk among first-degree relatives of women affected with preterm birth [35,36], placental abruption [11] and pre-eclampsia [14,37]; however, few of these studies have scaled the increase in risk among relatives by the population prevalence for a given pregnancy outcome (placental abruption [11], pre-eclampsia [37]), as done to calculate λ_S. Maternal recurrence risk, similar in calculation to the sib-sib OR, has previously been reported for these disorders [9,38-43]. Yet, only one study of preterm birth and PPROM [9] scaled maternal recurrence relative to population prevalence of the disorder and did not consider this measure as an indication of familial aggregation. λ_S and sib-sib OR, defining the infant of an affected pregnancy as proband, have not been reported for these disorders. Estimating λ_S, in which

the increased risk for a disorder is scaled by population prevalence, is particularly important, as population prevalence can vary by race. While there may be a significant increase in risk among siblings or a significant maternal recurrence risk, such a risk may reflect high population prevalence, rather than familial effects, *per se*. As a result, calculating λ_S may lead to different conclusions that those made by previous reports of maternal recurrence risk. Since individual demographic factors, such as socioeconomic status or body mass index, may also contribute to risk, we calculate sib-sib OR adjusted for important medical and environmental risk factors to assess to what extent genetic effects may account for familial aggregation.

In order to test whether genetic effects may influence these outcomes, our analyses define the infant of an affected pregnancy as the proband. We estimate λ_S and sib-sib OR to determine whether each outcome clusters in families.

Results
Preterm birth
The population risks for preterm birth at < 35 gestational weeks were estimated as 3.6%, 2.8%, and 7.8%, in all races, whites and blacks, respectively. Among second-born siblings in the sibling subcohort whose older sibling was affected, rates of preterm birth for all races, whites and blacks, respectively, were used to estimate the sibling risk (see Table 1). λ_S and its 95% CI were 4.3 (4.0–4.6), 4.4 (4.0–4.7), and 2.8 (2.6–3.1) for all races, whites, and blacks, respectively, indicating a significant increase in risk to siblings of preterm birth patients compared to the population.

Individuals whose older sibling was affected by preterm birth were also at significantly higher risk compared to individuals whose older sibling was unaffected (see Table 1). This increase in risk persisted after adjusting for known risk factors. Adjusted OR with 95% CI were 4.2 (3.9–4.5), 5.1 (4.6–5.7), and 3.3 (2.9–3.7) for all races, whites and blacks, respectively.

PPROM
The population risks for PPROM were estimated as 0.8%, 0.6% and 1.9%, in all races, whites and blacks, respectively. Among second siblings in the matched sibling sub-cohort whose older sibling was affected, rates of PPROM were used to estimate sibling risk (see Table 2). λ_S and its 95% confidence interval were 8.19 (6.50–9.88), 6.75 (4.59–8.91), and 6.40 (4.66–8.14) for all races, whites, and blacks, respectively, indicating a significant increase in risk to siblings of PPROM patients compared to the population.

Individuals whose older sibling was affected by PPROM were also at significantly higher risk compared to individuals whose older sibling was unaffected (see Table 2). This increase in risk persisted after adjusting for known risk factors. Adjusted OR with 95% CI were 9.6 (7.6–12.2), 8.5 (6.0–12.1), and 8.9 (6.4–12.5) for all races, whites and blacks, respectively.

Placental abruption
Population rates of placental abruption were estimated as 0.8%, 0.7%, 1.0%, in all races, whites and blacks respectively. Among second siblings in the matched sibling sub-cohort whose older sibling was affected, rates of placental abruption were used to estimate risk to siblings (see Table 3). λ_S and its 95% confidence interval were 3.95 (2.63–5.27) and 4.93 (3.18–6.68), for all races and whites, respectively, indicating a significant increase in risk to siblings of placental abruption patients compared to the population.

We found that individuals whose older sibling was affected by placental abruption were also at significantly higher risk compared to individuals whose older sibling was unaffected (see Table 3). This increase in risk persisted after adjusting for known risk factors. Adjusted OR with 95% CI: 3.8 (2.6–5.5) and 5.0 (3.4–7.4) for all races and whites, respectively. Blacks did not show a significant increase in risk to siblings of placental abruption births

Table 1: λ_S and sib-sib OR (with 95% CI) for preterm birth.

	All races	White	Black
Population: preterm birth	9759	6232	3354
Population: N	268103	220728	42899
Population risk	0.036 (0.035–0.037)	0.028 (0.027–0.029)	0.078 (0.075–0.081)
Siblings: sibpairs with both siblings affected	1020	514	489
Siblings: sibpairs with first sibling affected	6522	4181	2210
Sibling risk	0.156 (0.147–0.165)	0.123 (0.113–0.133)	0.221 (0.204–0.238)
λ_S	4.3 (4.0–4.6)	4.4 (4.0–4.7)	2.8 (2.6–3.1)
Sib-sib unadjusted OR (95% CI)	5.6 (5.2–6.0)	5.7 (5.2–6.3)	3.6 (3.2–4.0)
Sib-sib adjusted OR (95% CI)#	4.2 (3.9–4.5)	5.1 (4.6–5.7)	3.3 (2.9–3.7)

#Adjusted for mother < 20 years old, mother < 12 education, Medicaid (index of low SES), no prenatal care, mother BMI < 20 kg/m^2, cigarette smoking

Table 2: λ_S and sib-sib OR (with 95% CI) for PPROM.

	All Races	White	Black
Population: PPROM	2105	1311	763
Population: N	254740	211308	39190
Population risk	0.008 (0.008–0.008)	0.006 (0.006–0.006)	0.019 (0.018–0.020)
Siblings: sibpairs with both siblings affected	88	37	49
Siblings: sibpairs with first sibling affected	1300	883	393
Sibling risk	0.068 (0.054–0.082)	0.042 (0.029–0.055)	0.125 (0.092–0.158)
λ_S	8.2 (6.5–9.9)	6.8 (4.6–8.9)	6.4 (4.7–8.1)
Sib-sib unadjusted OR (95% CI)	10.8 (8.6–13.5)	8.8 (6.3–12.4)	8.8 (6.4–12.1)
Sib-sib adjusted OR (95% CI)#	9.6 (7.6–12.2)	8.5 (6.0–12.1)	8.9 (6.4–12.5)

#Adjusted for mother < 20 years old, mother < 12 education, Medicaid (index of low SES), no prenatal care, mother BMI < 20 kg/m^2, cigarette smoking

either compared to the population (λ_S = 1.64 (0.04–3.24)) or compared to siblings of births unaffected by this disorder (unadjusted OR: 1.4 (0.5–3.7), adjusted OR: 1.2 (0.4–3.9)).

Pre-eclampsia

Population rates of pre-eclampsia were estimated as 3.2%, 3.1%, and 4.1%, in all races, whites and blacks, respectively. Among second siblings in the matched sibling subcohort whose older sibling was affected, rates of pre-eclampsia were used to calculate sibling risk (see Table 4). λ_S and its 95% confidence interval were 4.51 (4.24–4.78), 4.52 (4.21–4.83), and 4.11 (3.59–4.63) for all races, whites, and blacks, respectively.

We found that individuals whose older sibling was affected by pre-eclampsia were also at significantly higher risk compared to individuals whose older sibling was unaffected (see Table 4). This increase in risk persisted after adjusting for known risk factors. Adjusted OR with 95% CI were 8.1 (7.5–8.8), 9.0 (8.2–9.8), and 5.8 (4.9–7.0) for all races, whites and blacks, respectively.

Discussion

We hypothesized that siblings of individuals who were products of pregnancies affected by one of several adverse outcomes, preterm birth, PPROM, placental abruption and pre-eclampsia, would be at increased risk for the same outcome. λ_S and sib-sib OR values significantly greater than one indicate that risk to siblings of adverse pregnancy outcome births is elevated compared to the population rate and to the rate in siblings of unaffected individuals, respectively. None of the 95% CI for λ_S or sib-sib OR values overlap with one, with the exception of placental abruption in blacks. The lack of evidence for familial aggregation of placental abruption in blacks may be explained by the rarity of the event and the relatively small racial subgroup (see Table 3). These data suggest that genetic and/or environmental risk factors shared among siblings affect these disorders.

Estimates of sib-sib OR are consistent with previous studies of maternal recurrence risk in the Missouri birth certificate database [38,39], and of maternal recurrence risk scaled to the population prevalence for preterm birth [9]. Our estimate of λ_S is noticeably smaller than the maternal recurrence risk, scaled by population prevalence of PPROM estimated in [9] (OR (95% CI): 20.6 (4.7, 90.2)).

Table 3: λ_S and sib-sib OR (with 95% CI) for placental abruption.

	All races	White	Black
Population: placental abruption	2050	1579	428
Population: N	268002	220641	42888
Population risk	0.008 (0.008–0.008)	0.007 (0.007–0.007)	0.010 (0.009–0.011)
Siblings: sibpairs with both siblings affected	34	30	4
Siblings: sibpairs with first sibling affected	1124	851	245
Sibling risk	0.030 (0.020–0.040)	0.035 (0.023–0.047)	0.016 (0–0.032)
λ_S	4.0 (2.6–5.3)	4.9 (3.2–6.7)	1.6 (0.0–3.2)
Sib-sib unadjusted OR (95% CI)	4.1 (2.9–5.8)	5.4 (3.8–7.9)	1.4 (0.5–3.7)
Sib-sib adjusted OR (95% CI)#	3.8 (2.6–5.5)	5.0 (3.4–7.4)	1.2 (0.4–3.9)

#Adjusted for mother < 20 or > 35 years old, mother < 12 education, Medicaid (index of low SES), no prenatal care, mother BMI < 20 kg/m^2, cigarette smoking, insulin-dependent diabetes mellitus, chronic hypertension, hydraminos/oligohydraminos

Table 4: λ_S and sib-sib OR (with 95% CI) for pre-eclampsia.

	All races	White	Black
Population: pre-eclampsia	8600	6749	1736
Population: N	267840	220505	42861
Population risk	0.032 (0.031–0.033)	0.031 (0.031–0.031)	0.041 (0.039–0.043)
Siblings: sibpairs with both siblings affected	1070	821	233
Siblings: sibpairs with first sibling affected	7384	5869	1400
Sibling risk	0.145 (0.137–0.153)	0.140 (0.131–0.149)	0.166 (0.146–0.186)
λ_S	4.5 (4.2–4.8)	4.5 (4.2–4.8)	4.1 (3.6–4.6)
Sib-sib unadjusted OR (95% CI)	9.2 (8.5–9.9)	10.0 (9.1–10.9)	6.7 (5.7–7.9)
Sib-sib adjusted OR (95% CI)#	8.1 (7.5–8.8)	9.0 (8.2–9.8)	5.8 (4.9–7.0)

#Adjusted for mother < 20 or > 35 years old, mother < 12 education, Medicaid (index of low SES), no prenatal care, mother BMI < 20 kg/m^2, cigarette smoking, insulin-dependent diabetes mellitus, chronic hypertension

This difference likely reflects the larger and population-based cohort used in our study, in contrast to [9] in which relatively small groups of PPROM (n = 114) and normal term (n = 208) deliveries were selected from a hospital population.

The utility of these measures lies primarily in establishing familial aggregation of a disorder, a prerequisite to claiming genetic influences on any trait. Yet, λ_S values may also be used to make tentative assessments of future genetic studies. The magnitude of λ_S values may reflect the mode of genetic etiology, influencing future studies' design. For example, for complex disorders, to which multiple genetic and environmental factors likely contribute, reported λ_S values range from 1.3–75, with peaks at 3–4 and 10–15 [31]; in contrast, monogenic Mendelian disorders show λ_S values an order of magnitude higher or more (eg. cystic fibrosis λ_S ~500 [30]). Thus, moderate values for λ_S, such as those reported for the adverse pregnancy outcomes studied (see tables 1, 2, 3, 4), are consistent with complex genetic and environmental etiologies. Among complex disorders, λ_S has been used to estimate the ability of a study to detect specific genes [44]. However, large values of λ_S do not necessarily predict linkage [31,45] or association [46] studies' success. Additionally, measures that reflect the strength of a genetic effect detected either by linkage, λ_S calculated with respect to a specific locus, or by association, genotype relative risk, γ, which measures the ratio of disease risks between individuals with and those without the susceptibility genotypes, have only an indirect correlation with λ_S[46]. Moderate λ_S values may correspond with high γ values (eg. rheumatoid arthritis [46]) and vice versa. While limitations in interpreting λ_S values exist, disorders with similar λ_S values to the adverse pregnancy outcomes reported here have had specific genes mapped (eg. hypertension, obesity [31]), suggesting that identification of specific genes influencing these conditions may be possible.

While the increased risk to siblings may be explained in part by shared genetics, some evidence suggests that multiple interacting environment factors can account for familial clustering [47]. Hence, the clustering of multiple non-genetic risk factors in families may account for these results. In order to distinguish genetic from other familial risk factors, we calculated sib-sib OR unadjusted and adjusted for important known environmental risk factors. Overall, the elevated risk to siblings persists after adjustment for such factors. While there may be important non-genetic factors affecting each outcome for which we have not accounted, we believe these results suggest that genetic influences may contribute to each of the adverse pregnancy outcomes studied.

Interestingly, λ_S and sib-sib OR estimates in blacks are generally smaller than those for whites. For PROM and pre-eclampsia, the 95% CI for λ_S and sib-sib OR estimates for the two racial groups overlap; however, these CI do not overlap for preterm birth or placental abruption. Hence, it is difficult to determine to what extent family clustering of these outcomes may differ among races. Differences in the magnitude of λ_S and sib-sib OR estimates between blacks and whites may be explained in part by the higher population prevalence for blacks compared to whites for each outcome studied (non-overlapping 95% CI, see tables 1, 2, 3, 4), which may reflect higher overall rates of genetic and/or environmental risk factors in this population.

The Missouri database provides many of this study's strengths. The large number of first recorded siblings in the population cohort (n = 267,472) and matched sibpairs in the sibling cohort (n = 163,826) provides a large sample size from which to estimate λ_S and sib-sib OR. Additionally, because this database represents a population cohort of births, rather than births selected based on any particular pregnancy outcome, biases due to ascertainment and overreporting, which can inflate λ_S values [48], should be minimal.

However, using a birth certificate database like this one also presents several limitations. First, complications of labor and delivery and maternal and infant medical conditions recorded in such databases may be underreported [49]; as a result, population and/or sibling risk for a particular disorder may be underestimated, potentially biasing our results. For example, the relative rarity of placental abruption in the population makes concordant sibships, particularly in blacks, rare, thereby reducing sample sizes for risk estimates for this disorder. Additionally, gestational age estimates contained in birth certificate databases are based primarily on the date of the last menstrual period, which may be recalled inaccurately or misclassified due to postconceptional bleeding [49], potentially influencing estimates of preterm birth and PPROM prevalence in this dataset. We also acknowledge that each of the categories of preterm birth that we analyzed may in themselves be rather heterogeneous. For example, initiation of spontaneous labor may result in preterm birth in each of the categories, though for some etiologies, particularly pre-eclampsia, iatrogenic delivery could contribute significantly. Our utilization of a more rigorous definition of preterm birth at less than 35 weeks should minimize the contribution of iatrogenic delivery. A final important limitation to this database is the limited amount of information on race. Maternal race is self-reported and possibly subject to population stratification and/or admixture. Additionally, information on paternal race is incomplete, further affecting the accuracy of infants' reported race.

The Missouri database also does not document relationships between mothers; as a result, similar calculations cannot be made to estimate familial clustering when the mother of an affected pregnancy is considered the proband. Moreover, the database contains little information on fathers, making it impossible to distinguish full from half siblings in most sibships. Because we cannot distinguish siblings that share both maternal and paternal factors from those that share maternal factors only, we cannot assess to what extent the increased risk can be attributed to factors unique to the fetus, rather than those shared with its mother. Due to these limitations, we cannot examine the relative importance of maternal versus fetal genetic effects, studied by Wilcox et al. [25] and Cnattingius et al. [17], for preterm birth and preeclampsia, respectively. Cnattingius et al. [17] reports 20% of variation in preeclampsia risk is due to fetal genetic effects and the combined effect of fetal genetic factors and couple effects are as important as maternal genetic effects. In contrast, Wilcox and colleagues [25] report only a weak association between father's family history and risk for preterm birth (RR (95% CI): 1.12 (1.01–1.25)), which became nonsignificant at earlier gestational ages (RR (95% CI): 1.06 (0.77–1.44). From this trend, the authors conclude that fetal genes may contribute to normal labor,

but, not preterm delivery [25]; however, Wilcox and colleagues [25] have relatively few early preterm offspring of early preterm mothers (n = 91) and fathers (n = 39) from which risk was estimated, and do not stratify based upon race/ethnicity. Similarly, a recent study [50] suggested that paternal genetics contributed little to gestational age, but could not refute the possible role of maternally-inherited genes expressed in the fetus. Hence, while paternally-inherited genes may contribute little to preterm birth or other disorders, maternally-inherited genes expressed in the fetus may still be important. Because of our study's limitations, we may be detecting effects due to shared uterine environment, shaped in part by maternal genes, rather than maternally-inherited genes in siblings. Hence, fetal genetic effects may make contributions of lesser magnitude than maternal genetic factors, with fetal genetic factors having a more prominent role in certain etiologies of preterm birth.

Conclusion

We have observed familial aggregation of preterm birth, PPROM, placental abruption and pre-eclampsia. Overall, siblings are at increased risk for each outcome, even after adjusting for important known environmental risk factors. While the influence of shared unmeasured environmental risk factors on sibling risk cannot, and should not, be discounted, we hypothesize that maternal and/or fetal genetic influences account for some of the increased risk to siblings observed. Moreover, though it is difficult to determine to what extent fetal and maternal effects overlap in these analyses, we postulate that fetal genetic factors may contribute to these disorders and suggest that they are studied further.

Methods
Study design
A protocol was approved by the Missouri Department of Health and Senior Services and by Washington University School of Medicine to analyze the state's maternally linked birth-death certificate database. We analyzed this database to assess the recurrence risk for a discrete group of adverse pregnancy outcomes, including preterm birth, preterm premature rupture of membranes (PPROM), placental abruption, and pre-eclampsia, in maternally-linked siblings. Births to the same mother were linked by a unique identifier called a sibship number, described elsewhere [51]. Full siblings and half-siblings resulting from pregnancies in the same mother were not distinguished. All protected health information with personal identifiers was removed before distributing the data for analysis.

This analysis was restricted to births that occurred between 1989 and 1997, since births that occurred before 1989 lacked complete medical and social histories. Fetal deaths occurring at < 20 weeks gestation, multiple gesta-

tion pregnancies and individuals with no maternally-linked siblings recorded in the database were excluded from this analysis. After excluding such cases, the remaining cohort consisted of 473,881 births, of which 383,812 (81.2%) were white and 81,889 (17.3%) were black. 267,472 births (220,728 (82.5%) white and 42,899 (16.0%) black) were the first maternally-linked sibling in the database and used to estimate the population prevalence for each outcome.

A second cohort of matched siblings was constructed from this dataset to analyze sibling risk for each outcome. The two oldest siblings born to the same mother during the study period were included. The dataset was not restricted to parity 0 and parity 1 women, in order to be as unbiased as possible in estimating risk for siblings and providing the best index of population prevalence. Additional siblings born to the same mother were excluded to simplify the statistical model. This cohort comprised of 327,652 matched siblings, of which 265,947 (81.2%) were white and 55,555 (17.0%) were black. Second-born siblings whose older sibling was affected by a particular outcome were used to estimate sibling risk for λ_S and sib-sib OR.

Definitions

Preterm birth is defined by the World Health Organization as delivery < 37 weeks [52]. To avoid inclusion of borderline gestational ages which may introduce misclassification bias, we defined preterm birth as delivery < 35 weeks in this study. Information from the last menstrual period and clinical data were used to calculate the best estimate of gestational age. PPROM was defined as births delivered < 35 weeks complicated by premature rupture of membranes. For PPROM, births complicated by pre-eclampsia, insulin-dependent and other diabetes, or eclampsia were excluded from analysis due to the potential for these births being delivered for medical reasons. First-born sibling and second-born sibling refer to the two oldest siblings recorded in database.

Statistical analysis

$$\lambda s = \frac{\text{P(affected|affected sibling)}}{\text{Population prevalence}}$$

λ_S was calculated as the frequency of an outcome in the individuals whose older sibling was affected with the disorder in the sibling cohort divided by the frequency of the outcome in first siblings in the larger cohort. 95% confidence intervals (CI) for sibling risk, population risk and sibling risk ratio were calculated by standard procedures for a binomial variable.

$$\text{Sib} - \text{sib OR} = \frac{\text{P(affected|affected sibling)}}{\text{P(affected|unaffected sibling)}}$$

Sib-sib OR was calculated as the odds of a child being affected with a particular adverse outcome, given that their older sibling was affected, divided by the odds of a child being affected with a particular adverse outcome, given that their older sibling was unaffected. Sib-sib OR were adjusted for known medical and environmental risk factors for the outcome to most conservatively estimate residual familial effects on risk. For preterm-birth and PPROM, OR were adjusted for: mother's age < 20 years old, mother < 12 years of education, recipient of state-funded assistance (an index of low socioeconomic status), no prenatal care, mother's body mass index (BMI) < 20 kg/m^2, and cigarette smoking during pregnancy. In addition to these risk factors, pre-eclampsia ORs were corrected for: mother's age > 35 years old, insulin-dependent diabetes mellitus, chronic hypertension. ORs for placental abruption were corrected for hydraminos/oligohydraminos in addition to the risk factors listed above.

Frequencies for λ_S and logistic regression analyses for the sib-sib OR were performed using Stata 9 [53]. Each calculation was made for preterm birth, PPROM, placental abruption, and pre-eclampsia in all races (including individuals whose race was neither black nor white), as well as stratified by black or white race. λ_S and sib-sib ORs calculated by race compare siblings of affected individuals designated as black or white to the siblings of unaffected individuals of the same race or the population prevalence for that race.

Authors' contributions

JP participated in the design of the study, carried out the statistical analyses, participated in interpreting results, and drafted the manuscript. IB participated in interpreting results and contributed to the manuscript. TM and DS participated in the design of the study, provided support for the statistical analysis, participated in interpreting results, and contributed to the manuscript. LJM conceived of the study, participated in its design and coordination, and contributed to the manuscript. All authors read and approved the final manuscript.

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