Inherited Predisposition to Spontaneous Preterm Delivery

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OBJECTIVE: To assess inherited predisposition to spontaneous preterm delivery.

METHODS: In this retrospective cohort study, intergenerational data on deliveries in mother–daughter pairs were analyzed from the Aberdeen Maternity Neonatal Databank using multilevel logistic regression. The study included an exposed cohort of all women born spontaneously preterm or whose mothers had experienced at least one spontaneous preterm delivery (at 24–37 weeks of gestation). The unexposed cohort included women who were born at term (after 37 weeks of gestation) or those whose mothers had never experienced any spontaneous preterm deliveries (24–37 weeks of gestation). The primary outcome was spontaneous preterm delivery in the daughters' pregnancies. Results are shown as adjusted odds ratios (ORs) and 95% confidence intervals (CIs).

RESULTS: We identified 22,343 pregnancies occurring in 13,845 daughters born to 11,576 mothers. Women who were born spontaneously preterm had significantly higher odds of delivering preterm babies (OR 1.49, 95% CI 1.12–1.99). A stronger association was seen when the analysis was restricted to nulliparous women who had been born spontaneously preterm (OR 1.60, 95% CI 1.16–2.21). Other predictors of a woman having a spontaneous preterm delivery were age at delivery younger than 20 years (OR 1.67, 95% CI 1.43–1.94), lower socioeconomic status (OR 1.22, 95% CI 1.04–1.44), smoking more than 10 cigarettes per day (OR 1.47, 95% CI 1.27–1.71), body mass index 19 kg/m^2 or less (OR 1.48, 95% CI 1.24–1.77), previous preterm delivery (OR 2.51, 95% CI 1.71–3.66). The risk of a woman delivering spontaneously preterm was increased even if her mother had a history of spontaneous preterm delivery in any other pregnancy (OR 1.35, 95% CI 1.12–1.63). The absolute risk of spontaneously delivering preterm in women who were born preterm was 9% as opposed to 6.2% in those who were born full-term. This gives an increase in risk of spontaneous preterm birth of 2.8% in women who were born spontaneously preterm.

CONCLUSION: Women born spontaneously preterm or with siblings delivered in a similar manner have an increased risk of spontaneous preterm delivery in their own pregnancies.

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See related editorial on page 1114.

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Preterm birth is the leading cause of perinatal morbidity and mortality[1] in the developed world, costing society $26 billion per year.[2] It accounts for 60% of deaths in babies and serious complications after delivery,[3] such as cerebral palsy. Spontaneous preterm birth refers to any delivery between 24 and 37 weeks of gestation in the absence of induced labor or elective cesarean delivery,[4] and it occurs in 7% of all deliveries in the United Kingdom.[5] Elsewhere, including the United States, it has been reported in 12% to 13% of all births, [6,7] representing an increase of 30% since 1981. A recent analysis of Scottish national data collected over the course of two decades shows an increase in spontaneous as well as elective or induced preterm birth.[8]

Current strategies to predict and prevent spontaneous preterm birth are compromised by gaps in our understanding of the etiopathogenesis of this condition. Although many causes of preterm birth have been identified, including infection (both genital and systemic) and multiple pregnancy, the reasons behind most spontaneous preterm births remain unknown.[9] Interventions for prevention of this condition have been unsuccessful, with the possible exception of cervical cerclage[1] and use of progesterone.[10,11]

Spontaneous preterm birth results from a complex interaction of genetic, environmental, social, and behavioral factors. Several lines of evidence support a genetic predisposition to spontaneous preterm birth.[12] A single spontaneous preterm birth has a 15% risk of recurrence in a future pregnancy, increasing to 32%[3] after two previous episodes. There is clear evidence of racial predisposition,[13] with blacks facing a 17% risk of spontaneous preterm birth as opposed to 10% in whites.[14] Spontaneous preterm birth can also run in families,[5] although the evidence surrounding this is conflicting.

A literature search on preterm birth and its recurrence across the generations was performed using Ovid MEDLINE and Embase databases (1990–2006). A number of studies were identified.[15–21] Most addressed the association between perinatal factors and preterm birth, but few explored intergenerational influences. In this retrospective cohort study, we hypothesized that women whose mothers had spontaneously given birth preterm were at higher risk for having a similar birth event in their own pregnancies.

PATIENTS AND METHODS

Our study was based on routinely collected data on all singleton deliveries occurring in mother–daughter pairs as recorded in the Aberdeen Maternity Neonatal Databank (http://www.abdn.ac.uk/amnd) using a retrospective cohort study design. The exposed cohort comprised women ("daughters") who were either born spontaneously preterm or had mothers who had had a spontaneous preterm delivery (24–37 weeks) in any pregnancy. The unexposed cohort included all women ("daughters") who were born at term (greater than 37 weeks of gestation) or whose mothers had never experienced any spontaneous preterm deliveries (24–37 weeks of gestation).

The primary outcome was spontaneous preterm delivery in the daughters' pregnancies. Because the mechanisms of preterm birth in twins and higher-order multiple pregnancies are potentially different from that of singletons, we excluded the former from all analyses. Women who had induction of labor or elective cesarean delivery were also excluded from the analysis.

After approval by the steering committee of the Aberdeen Maternity Neonatal Databank, who are the Caldicott guardians of the data, an anonymous data set was provided to the researchers. Because all analyses were performed on a data set stripped of identifiers, the North of Scotland Research Ethics Service was of the opinion that formal Ethics approval was not required. Our methods incorporated guidelines[12] based on a review of genetic epidemiologic studies of preterm birth.

Within the Scientific Information Retrieval system used for data capture, relatives are identified as mother–daughter pairs by matching the mother's surname and date of delivery to the daughter's maiden name and date of birth. New York State Identification and Intelligence Systems (Albany, NY, 1970) and SOUNDEX (Russell and Odell, 1918) were utilized for identifying names that are similar. Whereas probability matching is utilized for the matching of names, only exact matches are accepted for the dates of birth. The data set used for this study recorded deliveries in two generations between September 1948 and March 2008. Since the inception of the Aberdeen Maternity Neonatal Databank, the numbers of such intergenerational pairs have increased and now include data on older women who gave birth several decades ago. It is now feasible to identify three-generation families, because those women identified as daughters have now become mothers, thus enabling identification of grandmothers and granddaughters. The current limitation of linkages over three generations is that the data set is somewhat biased toward women who reproduce early in life because their pregnancy details are inevitably available earlier than those for women who have children later in life.

Gestational age is recorded as a continuous variable according to the date of the last menstrual period as reported by women and then confirmed or refuted by ultrasonography (since 1986). Because most of the data pre-date routine use of ultrasound scans in pregnancy, gestational age is mostly calculated according to dates. This variable was recoded, for some analyses, into a binary variable, ie, those who were born preterm, (before 37 completed weeks of gestation) and those who were not. Certainty of gestation is recorded in more than 99% of women and works as a data quality check.

Since its inception, data have been concurrently entered into the Aberdeen Maternity Neonatal Databank. Labor is classified as spontaneous, induced, or elective cesarean delivery without labor. Reasons for induction of labor are clearly documented according to a prespecified code.

The classification of preeclampsia is based on the classification of hypertensive disorders of pregnancy by Davey and MacGillivray,[22] which has been used throughout in the Aberdeen Maternity Neonatal Databank. Before the publication of this article, Nelson's[23] classification was used. The two classification systems are very similar and, for purposes of epidemiological analyses, may be used interchangeably.

Gestational hypertension is defined as a diastolic blood pressure of 110 mm Hg or more on any one occasion or diastolic blood pressure of 90 mm Hg or more on any two or more occasions at least 4 hours apart. Preeclampsia is defined as hypertension with proteinuria of 300 mg/24 hours or more or proteinuria found in two urine specimens collected at least 4 hours apart. Birth weight is recorded (in grams) as a continuous variable in the Aberdeen Maternity Neonatal Databank.

Social class is based on the husband's or partner's occupation and coded in the Aberdeen Maternity Neonatal Databank according to the British Registrar General's occupational social class classification of 1951, for which there are six categories: I, professional; II, managerial; III, skilled nonmanual; IV, skilled manual; V, semi-skilled; and VI, unskilled. Women's own social classes were used when there was no available information for the partner.

Body mass index is calculated using the formula weight in kilograms divided by height in meters squared. The height and weight used are those measured and recorded by clinical staff at the first antenatal booking visit at less than 20 weeks of gestation. Other variables include self-reported smoking habits (recorded during antenatal clerking as the number of cigarettes smoked per day).

Because of the nature of the ethnic population resident in the northeast of Scotland over the past 60 years, this cohort comprises white women only. Thus, ethnicity is not considered as a covariate in the analyses.

All statistical analyses were performed using STATA version 11 (StataCorp, College Station, TX). The initial analyses were performed on nulliparous women, and a multiple logistic regression model was used to examine the relationship between a woman's (daughter's) characteristics and the chance of her having a spontaneous preterm birth. We adjusted for confounding variables such as the woman's age at delivery, social class, smoking, preeclampsia, and history of preterm delivery. The analysis was stratified by parity. Mixed-effect modeling[24] was used to allow for the clustering of pregnancies within daughters, daughters within mothers, and so on. Although each woman could have had several pregnancies, the characteristics of her mother and grandmother would remain unchanged for each of them. Therefore, pregnancies were nested within women (daughters) who were themselves nested within their mothers. Because the primary outcome (spontaneous preterm birth) was binary, a multilevel logistic regression analysis was used to examine the interrelationship between a daughter's characteristics and her mother's and grandmother's characteristics at the time of the daughter's birth, and the risk of spontaneous preterm birth in the daughter. Specifically, a two-level hierarchical analysis was used to explore the interrelationship between a daughter's pregnancy-related characteristics, her mother's characteristics at the time of her (the daughter's) birth, and the probability of spontaneous preterm birth in the daughter. The strength of association of each characteristic is reported using unadjusted and then multiadjusted odds ratios (ORs) and 95% confidence intervals (CIs). For each variable, missing values were kept as a separate category to maximize numbers and the resultant statistical power for analysis.

Potential confounders were included at two levels and coded for daughters and mothers. For daughters, age at delivery (19 or younger, 20–35, and 36 years or older), social class (groups I to III and groups IV and V), and smoking status (none, 1–9 cigarettes/day, and 10 or more cigarettes/day) were recorded. Body mass index at examination (19 or less, 20–24, 25–29, and 30 or greater)[24] and hypertensive disorders of pregnancy (coded into three groups: none, preeclampsia, and gestational hypertension), spontaneous preterm birth, history of miscarriage, and history of preterm delivery and parity (all yes and no) were also included.

For mothers, age at delivery (19 or younger, 20–35, and 36 years or older), social class (groups I to III and groups IV and V), preeclampsia (coded into three groups: yes, no, and gestational hypertension), preterm birth of any daughter (yes and no), preterm birth of index daughter (yes and no), and history of miscarriage and parity were included.

STATA version 10 was used for the analysis; $P \leq .05$ was used to denote statistical significance throughout.

RESULTS

A total of 35,096 pregnancy records of women (daughters) were available for analysis. Because our

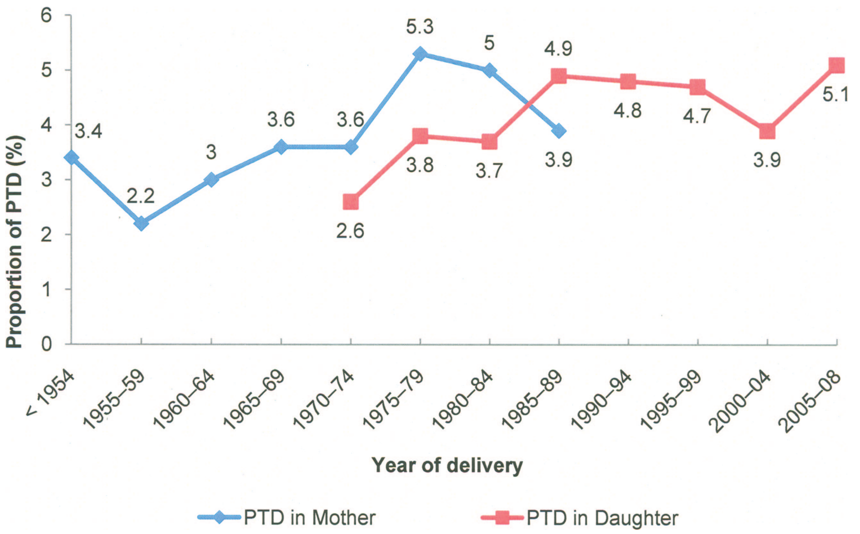

Fig. 1. Time trends of preterm delivery in mothers and their daughters. PTD, preterm delivery.

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focus was on spontaneous preterm birth, deliveries after induced labor (n=9,521) and elective cesarean delivery (n=1,716) were excluded. Pregnancy records that lacked information about gestational age in deliveries occurring in mothers (n=2,103) and mode of deliveries in daughters (n=108) were also excluded. Thus, 22,343 pregnancy records including 13,845 daughters born to 11,576 mothers were considered

Table 1. Comparison of Sociodemographic and Pregnancy Characteristics in Nulliparous Daughters Who Were Born Spontaneously Preterm (Exposed Cohort) or Full-Term (Unexposed Cohort)

Daughter Characteristics in the First Pregnancy	Daughter Born Spontaneously Preterm (n=471)	Daughter Born Full-Term (n=13,374)	Crude OR (95% CI)	Adjusted OR* (95% CI)
Age at delivery (y)				
19 or younger	44 (9.3)	1,238 (9.3)	1.56 (1.26–1.93)	1.33 (1.07–1.65)
20–35	407 (86.4)	11,455 (85.7)	1.00	1.00
36 or older	20 (4.3)	681 (5.1)	1.24 (0.92–1.67)	1.42 (1.04–1.95)
Social class				
I to III	81 (17.2)	3,403 (25.4)	1.00	1.00
IV and VI	390 (82.8)	9,971 (74.6)	1.37 (1.15–1.64)	1.19 (0.99–1.43)
Smoker				
No	186 (39.5)	5,811 (43.5)	1.00	1.00
1–9 cigarettes/day	41 (8.7)	1,022 (7.6)	1.56 (1.19–2.04)	1.45 (1.11–1.90)
10 or more cigarettes/day	174 (36.9)	3,962 (29.6)	1.81 (1.54–2.14)	1.70 (1.43–2.02)
Missing	70 (14.9)	2,579 (19.3)	1.09 (0.88–1.35)	1.06 (0.85–1.32)
Body mass index (kg/m^2)				
19 or less	52 (11.0)	1,342 (10.0)	1.51 (1.21–1.88)	1.43 (1.15–1.80)
20–24	218 (46.3)	6,535 (48.9)	1.00	1.00
25–29	105 (22.3)	2,952 (22.1)	1.03 (0.84–1.22)	1.03 (0.85–1.24)
30 or greater	52 (11.0)	1,224 (9.2)	0.92 (0.70–1.21)	0.93 (0.71–1.23)
Missing	44 (9.3)	1,321 (9.9)	1.46 (1.07–1.84)	1.35 (1.07–1.71)
HDP				
No	404 (85.8)	11,445 (85.6)	1.00	1.00
Gestational hypertension	58 (12.3)	1,602 (11.9)	0.82 (0.64–1.03)	0.85 (0.67–1.08)
Preeclampsia	9 (1.9)	327 (2.5)	1.46 (0.99–2.17)	1.53 (1.03–2.28)
Spontaneous preterm delivery				
No	428 (90.9)	12,616 (94.3)	1.00	1.00
Yes	43 (9.1)	758 (5.7)	1.67 (1.21–2.31)	1.60 (1.16–2.21)

OR, odds ratio; CI, confidence interval; HDP, hypertensive disorders of pregnancy.
Data are n (%).
* Simultaneously adjusted for all factors listed.

for analysis. Figure 1 shows the increase in prevalence of preterm birth over time in mothers and the daughters in the cohort.

Table 1 presents details of the daughters' first pregnancies and compares sociodemographic and pregnancy characteristics of those who were spontaneously born preterm with those who were not. Daughters born spontaneously preterm were more likely to belong to social classes IV and V, to smoke 10 or more cigarettes per day, and to have a body mass index of less than 20 kg/m^2. After simultaneous adjustment for all of these factors, the adjusted OR for spontaneous preterm delivery in a first pregnancy in daughters who were born preterm spontaneously was 1.60 (95% CI 1.16–2.21).

A separate analysis of all pregnancies occurring in daughters was performed using a two-level hierarchical model. Table 2 presents univariable and multivariable comparisons of the sociodemographic and pregnancy characteristics between daughters who were born preterm and those who were born full-term. Age at delivery, social class, smoking, and body mass index were all significantly different in the exposed and unexposed groups. Moreover, women who were born spontaneously preterm were more likely to experience a similar delivery (9.0% compared with 6.2%).

In daughters born spontaneously preterm, the adjusted odds of having a spontaneous preterm birth was 1.49 (95% CI 1.12–1.99). Other factors associated with a risk of spontaneous preterm birth were delivery age younger than 20 years (adjusted OR 1.67, 95% CI 1.43–1.94), lower socioeconomic class (adjusted OR 1.22, 95% CI 1.04–1.44), smoking 10 or more cigarettes per day (adjusted OR 1.47, 95% CI 1.27–1.71), and body mass index less than 20 kg/m^2 (adjusted OR

Table 2. Comparison of Sociodemographic and Pregnancy Characteristics in Daughters Born Spontaneously Preterm and Daughters Born Full-Term, Including All Daughter Pregnancies

Daughter Characteristics at Each Pregnancy	Daughter Born Spontaneously Preterm (n=798)	Daughter Born Full-Term (n=21,545)	Crude OR (95% CI)	Adjusted OR* (95% CI)
Age at delivery (y)				
19 or younger	134 (16.8)	3,068 (14.2)	1.89 (1.61–2.23)	1.67 (1.43–1.94)
20–35	639 (80.1)	17,732 (82.3)	1.00	1.00
36 or older	25 (3.1)	745 (3.5)	1.25 (0.88–1.77)	1.37 (0.99–1.89)
Social class				
I to III	121 (15.2)	4,899 (22.7)	1.00	1.00
IV and VI	677 (84.8)	16,646 (77.3)	1.52 (1.29–1.82)	1.22 (1.04–1.44)
Smoker				
No	287 (36.0)	8,647 (40.1)	1.00	1.00
1–9 cigarettes/day	66 (8.3)	1,675 (7.8)	1.47 (1.14–1.90)	1.22 (0.97–1.55)
10 or more cigarettes/day	318 (39.8)	6,772 (31.4)	1.83 (1.56–2.15)	1.47 (1.27–1.71)
Missing	127 (15.9)	4,451 (20.7)	1.27 (1.06–1.53)	1.17 (0.99–1.39)
Body mass index (kg/m^2)				
19 or less	101 (12.7)	2,366 (11.0)	1.64 (1.34–2.02)	1.48 (1.24–1.77)
20–24	377 (47.2)	10,590 (49.2)	1.00	1.00
25–29	154 (19.3)	4,355 (20.2)	0.97 (0.81–1.17)	1.01 (0.86–1.19)
30 or greater	73 (9.1)	1,660 (7.7)	0.88 (0.67–1.16)	0.96 (0.75–1.22)
Missing	93 (11.7)	2,574 (11.9)	1.86 (1.52–2.26)	1.57 (1.31–1.87)
Previous miscarriage				
No	724 (90.7)	19,548 (90.7)	1.00	1.00
Yes	74 (9.3)	1,997 (9.3)	0.82 (0.64–1.03)	1.04 (0.85–1.28)
Previous preterm delivery				
No	755 (94.6)	20,626 (95.7)	1.00	1.00
Yes	43 (5.4)	919 (4.3)	1.98 (1.28–3.06)	2.51 (1.71–3.66)
HDP				
No	657 (82.3)	18,172 (84.3)	1.00	1.00
Gestational hypertension	121 (15.2)	2,878 (13.4)	0.63 (0.51–0.78)	0.66 (0.55–0.81)
Preeclampsia	20 (2.5)	495 (2.3)	1.32 (0.89–1.96)	1.29 (0.90–1.83)
Preterm delivery				
No	726 (91.0)	20,204 (93.8)	1.00	1.00
Yes	72 (9.0)	1,341 (6.2)	1.62 (1.13–2.33)	1.49 (1.12–1.99)

OR, odds ratio; CI, confidence interval; HDP, hypertensive disorders of pregnancy.
* Simultaneously adjusted for all factors listed.

1.48, 95% CI 1.24–1.77). History of spontaneous preterm birth (adjusted OR 2.51, 95% CI 1.71–3.66) was also associated with a higher chance of spontaneous preterm birth in the next ongoing pregnancy.

We next investigated whether women whose mothers had one or more spontaneous preterm births were more likely to deliver preterm themselves. To do this, the cohort was divided into two groups based on whether a mother had a history of spontaneous preterm birth in any pregnancy. Table 3 presents the comparison of sociodemographic and pregnancy characteristics between the exposed (mothers with spontaneous preterm birth) and unexposed (mothers without spontaneous preterm birth) cohorts. The risk of spontaneous preterm birth was increased in daughters whose mothers had a history of a similar type of delivery in any pregnancy (crude OR 1.72, 95% CI 1.23–2.41) and remained statistically significant after adjusting for confounding factors, including a previous preterm delivery of the daughter (adjusted OR 1.35, 95% CI 1.12–1.63). The absolute risk of spontaneously delivering preterm in women who were born preterm was 9% as opposed to 6.2% in those who were born full-term. This gives an increase in risk of spontaneous preterm delivery of 2.8% in women who were born spontaneously preterm.

Table 3. Comparison of Sociodemographic and Pregnancy Characteristics in Mothers Who Had a Spontaneous Preterm Delivery in Any Pregnancy (Exposed Cohort) and Mothers With No History of a Spontaneous Preterm Delivery (Unexposed Cohort)

Daughter Characteristics	Mother Had Spontaneous Preterm Delivery in Any Pregnancy (n=1,846)	No History of Spontaneous Preterm Delivery in Mother (n=20,497)	Crude OR (95% CI)	Adjusted OR* (95% CI)
Age at delivery (y)				
19 or younger	318 (17.2)	2,884 (14.1)	1.89 (1.61–2.23)	1.42 (1.22–1.65)
20–35	1,476 (79.9)	16,895 (82.4)	1.00	1.00
36 or older	52 (2.8)	718 (3.5)	1.25 (0.88–1.77)	1.44 (1.05–1.96)
Social class				
I to III	296 (16.0)	4,724 (23.1)	1.00	1.00
IV to VI	1,550 (83.9)	15,773 (76.9)	1.52 (1.29–1.82)	1.20 (1.03–1.40)
Smoker				
No	671 (36.4)	8,263 (40.3)	1.00	1.00
1–9 cigarettes/day	154 (8.3)	1,587 (7.7)	1.47 (1.14–1.90)	1.20 (0.96–1.50)
10 or more cigarettes/day	715 (38.7)	6,375 (31.1)	1.83 (1.56–2.15)	1.47 (1.28–1.69)
Missing	306 (16.6)	4,272 (20.8)	1.27 (1.06–1.53)	1.17 (0.99–1.38)
Body mass index (kg/m^2)				
19 or less	226 (12.2)	2,241 (10.9)	1.64 (1.34–2.02)	1.45 (1.23–1.73)
20–24	912 (49.4)	10,055 (49.1)	1.00	1.00
25–29	350 (19.0)	4,159 (20.2)	0.97 (0.81–1.17)	1.02 (0.87–1.20)
30 or greater	142 (7.7)	1,591 (7.7)	0.88 (0.67–1.16)	1.00 (0.79–1.27)
Missing	216 (11.7)	2,541 (11.9)	1.86 (1.52–2.26)	1.45 (1.22–1.72)
Multiparous				
No	301 (16.3)	7,578 (36.9)	1.00	1.00
Yes	1,545 (83.7)	12,919 (63.0)	0.71 (0.62,0.81)	0.63 (0.55–0.72)
Previous miscarriage				
No	1,671 (90.5)	18,601 (90.8)	1.00	1.00
Yes	175 (9.5)	1,896 (9.3)	1.09 (0.88–1.35)	1.24 (1.01–1.52)
Previous preterm delivery				
No	1,755 (95.1)	19,626 (95.8)	1.00	1.00
Yes	91 (4.9)	871 (4.3)	1.98 (1.28–3.06)	3.95 (2.86–5.46)
HDP				
No	1,570 (85.1)	17,259 (84.2)	1.00	1.00
Gestational hypertension	231 (12.5)	2,768 (13.5)	0.63 (0.51–0.78)	0.63 (0.52–0.76)
Preeclampsia	45 (2.4)	470 (2.3)	1.32 (0.89–1.96)	1.18 (0.84–1.66)
Preterm delivery				
No	1,691 (91.6)	19,239 (93.8)	1.00	1.00
Yes	155 (8.4)	1,258 (6.1)	1.72 (1.23–2.41)	1.35 (1.12–1.63)

OR, odds ratio; CI, confidence interval; HDP, hypertensive disorders of pregnancy.
* Simultaneously adjusted for all factors listed.

DISCUSSION

Spontaneous preterm birth was more likely to occur in women (daughters) who were born spontaneously preterm or who had siblings who were. Other risk factors for spontaneous preterm birth in a woman (daughter) included the following: age younger than 20 years at delivery, lower social class, smoking, body mass index less than 20 kg/m^2, and history of spontaneous preterm birth.

Aberdeen, in the northeast of Scotland, offers a unique opportunity to perform longitudinal studies. It has a stable population with low levels of out-migration.[26] Obstetric details for all women within a defined geographical area are logged into the Aberdeen Maternity Neonatal Databank. Established in 1950, the Aberdeen Maternity Neonatal Databank holds population-based data on obstetric events for all women resident in Aberdeen city district, including reliable and detailed information on more than 35,000 mother– daughter pairs. Consistent coding criteria are used and intermittent checks are performed to ensure data quality.[27] The data collected allow researchers to distinguish between spontaneous and iatrogenic preterm labor. None of the studies identified on an extensive literature search has been able to adjust for conditions, such as preeclampsia, that have established intergenerational associations and can result in iatrogenic or spontaneous preterm delivery. The current analysis takes into account the clustering of events within individual women as well as in families, thereby making the results more robust and easier to interpret, without any loss of power. We were unable to stratify the risks of very preterm delivery (less than 32 weeks of gestation) compared with late preterm delivery because there were insufficient cases of the former in our data set to allow a meaningful breakdown of the data.

The main limitations of this study relate to its retrospective longitudinal nature. The data have been collected over six decades that have witnessed substantial changes in clinical practice, especially neonatal intensive care. This is reflected in the difference in proportion of preterm deliveries recorded in the two generations. Over the years, access to better neonatal and pediatric care has increased the chances of women born preterm living to adulthood and having pregnancies of their own. The Aberdeen Maternity Neonatal Databank only has pregnancy records of daughters who have had a pregnancy themselves and excludes any who may have been born preterm but have not lived long enough to bear children. This may also partially explain the increased rates of preterm delivery in daughters, which could introduce a degree of ascertainment bias. The other limitation of this study concerns the definition of "preterm delivery." Because much of our data predate routine use of ultrasonography, the gestational age and, therefore, the definition of preterm delivery, have been based on self-reported dates of the last menstrual period.

There have been few intergenerational studies on spontaneous preterm birth. Porter and Fraser[18] reported the odds (95% CI) of spontaneous preterm birth in white women who were delivered prematurely as 1.18 (95% CI 1.02–1.37). However, these data were obtained through birth certificate records; detailed obstetric information was lacking and inaccuracies in documenting gestation and birth weight cannot be ruled out. Cesarean deliveries (including emergency cesarean deliveries in women in preterm labor) were systematically excluded, possibly resulting in loss of a significant amount of data and possibly introducing potential bias. The study included 1,405 mothers who were born spontaneously preterm and 2,781 who were not. This study, which was based on a larger sample and was able to adjust for confounding factors, found a stronger association between being born spontaneously preterm and subsequent risk of experiencing a spontaneous preterm birth.

Winkvist and Mogren[20] analyzed gestational length and types of growth restriction in 4,746 generation pairs and found a trend toward an increased risk of any kind of preterm birth (OR 1.82, 95% CI 0.87–3.82) in daughters who had been small for gestational age but not those born preterm (OR 1.10, 95% CI 0.69–1.76). This study was unable to distinguish spontaneous from induced preterm labor. Data were extracted from obstetric medical notes, but confounders such as smoking and body mass index were not taken into account.

Selling et al[19] showed that after adjustment for body mass index, smoking, and socioeconomic status, women younger than 28 years who had been born small for gestational age were at increased risk of having a small-for-gestational age neonate (OR 2.68, 95% CI 2.11–3.41) but not for preterm birth (OR 1.08, 95% CI 0.70–1.64), spontaneous or induced. This study had a sample size of 807 daughters who were born preterm.

Differences in study populations and outcomes measured in these studies make a direct comparison with our findings difficult. Nevertheless, in contrast to the studies by Winkivist et al[20] and Selling et al,[19] in our study we found a definite increased risk of spontaneous preterm birth in women whose mothers had a similar type of delivery. Unlike these studies, we did not look at the intergenerational effect of growth restriction on preterm delivery.

More recently, in a study based on data from the Norwegian Birth Registry, Wilcox et al[28] investigated the risk of preterm birth in the female offspring, in which either the mother or the father was born preterm. The relative risk of preterm delivery in a daughter was 1.54 (95% CI 1.42–1.67) if the mother was born preterm and slightly less if the father was born preterm. The analysis was restricted to first deliveries only. The main analysis included all preterm deliveries, both spontaneous and induced; however, when induced preterm deliveries were excluded, the association was strengthened. The risks of preterm delivery inherited from the mother reported in this Norwegian study are more consistent with our findings.

Previous publications resulting from analysis of the intergenerational cohort within the Aberdeen Maternity Neonatal Databank were restricted in the numbers[29] of mother–daughter pairs. For example, only 505 mother–daughter pairs were available for analysis in this study looking at inheritance of birth weight in which a small inherited influence was demonstrated.[29]

Management of spontaneous preterm labor has mainly relied on interventions to delay delivery long enough to allow antenatal corticosteroid administration. Although these have reduced perinatal mortality and morbidity, it is necessary to understand the causes of spontaneous preterm birth and identify populations at risk before any targeted therapeutic interventions can be planned. Accurate prediction of risk may help in planning appropriate antenatal care in women deemed to be at high risk. Our study adds to the general body of epidemiological evidence suggesting genetic predisposition to preterm birth and highlights the inherited contribution toward spontaneous preterm birth in the context of known environmental factors, like smoking and social class. Recent publications have identified pathways for epigenetic regulation of spontaneous preterm birth. Changes in the expression of specific micro-RNAs in the myometrium in spontaneous labor at term have also been demonstrated[30] to help explain the biological mechanism of spontaneous preterm birth. Further research should focus on the identification of candidate genes for the condition, effects of "imprinting" via factors responsible for preterm birth in the previous generation, and efficacy of interventions such as progesterone in women at high risk.

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