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Fetal Constraint as a Potential Risk Factor for Craniosynostosis

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Abstract

Non-syndromic craniosynostosis is multifactorial, and fetal head constraint has been hypothesized as one factor thought to play a role. Data from the National Birth Defects Prevention Study (NBDPS), a large multi-site case-control study of birth defects, were used to evaluate associations between 4 selected factors related to fetal constraint and craniosynostosis: plurality (twins or higher), macrosomia (birth weight > 4000 g), post-term gestational age (≥42 weeks), and nulliparity (no previous live births). Case infants (n=675) had craniosynostosis documented either by radiographic evidence or by surgical intervention. Infants with a recognized or strongly suspected single-gene conditions or chromosomal abnormalities were excluded. Control infants (n=5,958) had no major birth defects and were randomly selected from the same population as case infants. Logistic regression was used to estimate odds ratios for the association between these 4 factors and craniosynostosis, while adjusting for several covariates. We found that plurality and nulliparity were associated with a two fold increased risk for metopic craniosynostosis, and macrosomia had almost twice the risk of developing coronal craniosynostosis. Contrary to our hypothesis, prematurity and low birth weight were also associated with craniosynostosis. In conclusion, these 4 constraint-related factors were not found to be associated with craniosynostosis when all suture types were combined, though some types of craniosynostosis were associated with individual constraint-related factors.

Keywords

Craniosynostosis; Fetal Constraint; Plurality; Twinning; Macrosomia; Prolonged Gestation; Low Birth Weight; Calvarial Morphogenesis; Skull deformation; Sagittal Synostosis; Metopic Synostosis

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INTRODUCTION

Craniosynostosis results from the premature fusion of one or more sutures between adjacent calvaria. It is most often an isolated finding in an otherwise normal child. In non-syndromic craniosynostosis, it has been difficult to decipher the underlying causes of premature suture fusion. Several risk factors have been implicated in craniosynostosis including fertility treatments [Kallen and Robert-Gnansia 2005; Reefhuis et al., 2003], higher antenatal maternal altitude of residence [Alderman et al., 1995], maternal thyroid disease [Rasmussen et al., 2007], paternal occupation [Bradley et al., 1995], and teratogenic exposures such as heavy maternal smoking that continued into the second trimester [Carmichael et al., 2008] and sodium valproate [Lajeunie et al., 2001].

Case reports and retrospective series led previous investigators to hypothesize that fetal head constraint might reduce dural growth stretch and thereby increase the risk of non-syndromic craniosynostosis [Graham et al., 1980; Graham et al., 1979; Graham and Smith 1980; Higginbottom et al., 1980]. Proposed constraint factors have included early descent of the fetal cranium into the lower uterine segment, breech presentation, maternal uterine malformation, nulliparity, oligohydramnios, multiple gestation (twins or higher), macrosomia and prolonged gestation.

It is well accepted that primary microcephaly or aggressively-shunted hydrocephalus [Cinalli et al., 1998; Weinzweig et al., 2008] can each result in secondary premature sutural fusion. One suggested mechanism for craniosynostosis involves altered dural mechanical signaling, which is proposed to lead to premature fusion when dural growth stretch is decreased [Cohen 1991]. Given the above examples of postnatal influences on premature suture fusion, it is plausible that a deformational influence on the fetal calvaria in late gestation may account for a subset of craniosynostosis cases. Supporting evidence from animal models have shown that *in vivo* constraint-induced suture fusion causes changes in expression of genes involved in cranial ossification [Heller et al., 2007; Jacob et al., 2007]. Not only is there an induction of suture obliteration but also an induced expression of osteogenic bone growth factors (such as TGF beta) in fetal calvarial bone and the underlying dura, suggesting that mechanical factors might influence the expression of genes involved in cranial ossification and suture fusion.

To date, no population–based study has directly assessed the association between factors affecting fetal constraint and non-syndromic craniosynostosis. With a goal to clarify the role of fetal constraint for craniosynostosis risk, we assessed four available factors (birth weight, gestational age, multiple gestation, and parity) as proxies for potential fetal constraint.

METHODS

We used data from the National Birth Defects Prevention Study (NBDPS). Eligible subjects had estimated dates of delivery (EDDs) from October 1, 1997, to December 31, 2004. The NBDPS is a large, ongoing, multi-site case-control study of over 30 major birth defects conducted in 10 states within the United States. Detailed study methods have been published [Yoon et al., 2001]. Each state randomly selects between 125 and 150 liveborn infants without major birth defects (controls) per study year from birth certificates (AR 2000–2004, GA 2001–2004, IA, MA, NC, NJ, UT) or from birth hospitals (AR 1997–1999, CA, GA 1997–2000, NY, TX) with the goal of conducting 100 interviews to represent the population from which cases were derived. Clinical diagnostic information was abstracted from medical records and entered into a standardized database. A clinical geneticist from each site reviewed the diagnostic information to determine study eligibility of each case infant [Rasmussen et al., 2003]. For this analysis, case infants had a diagnosis of craniosynostosis

documented by either radiographic confirmation or by surgical intervention, excluding those with known or suspected chromosomal abnormalities or recognizable single-gene conditions. Data on infants with craniosynostosis from all study sites were subsequently reviewed by a single clinical geneticist (SAR) to ensure eligibility criteria were met and to classify each case as either “isolated” (if there was no other major defect or only minor defects) or as “multiple” (if there was one or more additional major, unrelated defect) [Rasmussen et al., 2003]. For each case infant, the specific synostotic suture involved was categorized as sagittal, coronal, metopic, lambdoid, unknown, or multiple. Infants with involvement of more than one type of suture were categorized as multiple sutures.

Maternal interviews were conducted primarily by telephone (in English or Spanish) using a standardized, computer-based questionnaire, no earlier than six weeks and no later than 24 months after the infant’s EDD. Final EDD was based on the mother’s self-report; if unknown, EDD was estimated from information in the medical record (less than two percent of subjects). Interviews were conducted with mothers of 675 cases (74% of eligible subjects) and 5,958 controls (69% of eligible subjects). The mean time from delivery to interview was 14 months for case mothers and 9 months for control mothers.

Factors considered as potentially conferring fetal constraint included multiple gestation, macrosomia (birth weight ≥4000 g), prolonged gestational age (≥42 weeks), and nulliparity (no previous live births). Covariates included maternal and paternal age (in years), maternal race-ethnicity (Caucasian, African American, Hispanic, Other), education (<12 years, 12 years or >12 years), pre-pregnancy body mass index (calculated as pre-pregnancy weight in kilograms divided by height in meters squared), infant sex, maternal smoking (during the month before pregnancy or the first trimester), gestational diabetes, and fertility treatment. Fertility treatment was defined as an affirmative answer to the following question: “Did you or [baby’s name]’s father take any medication or have any procedures to help you become pregnant? Data were examined with and without exclusion of women who had fertility treatments.

We excluded infants whose mothers had pre-pregnancy diabetes from all analyses (5 cases and 30 controls) because of the strong association between maternal diabetes and birth defects [Correa et al., 2008]. In addition, we excluded infants from multiple gestations from all analyses (32 cases and 141 controls), except the analyses of plurality, because infants born as part of a multiple gestation have been shown to be at increased risk of being born with a birth defect [Glinianaia et al., 2008]. Of note, all sets of twins were discordant for craniosynostosis, and no two subjects from the same gestation were used in the analysis. Using logistic regression models, we examined the association between each constraint-related factor and craniosynostosis. We examined crude odds ratios and odds ratios adjusted for the covariates listed above. In addition, we examined the association of plurality with craniosynostosis after excluding women who had fertility treatments. We estimated odds ratios and corresponding 95% confidence intervals using SAS (version 9.1, 2003, SAS Institute, Cary, NC). In addition, we also performed the analyses restricted to isolated cases and to subjects with no first-degree relative (i.e., a parent or sibling) with craniosynostosis.

RESULTS

After exclusion of subjects whose mothers had pre-pregnancy diabetes, there were 670 case infants and 5,928 control infants available for analysis. A summary of characteristics of the infants with craniosynostosis and control infants is provided in Table I and Table II. Cases were more likely than controls to be male (66% versus 50%, p value <0.001) and case mothers were more likely than control mothers to be non-Hispanic white (74% versus 60%, p value <0.001). When all suture types were analyzed together, and analyses were adjusted

for covariates, none of the constraint-related factors were associated with craniosynostosis, but low birth weight, as well as preterm delivery, were associated with increased risk (See Table III).

Suture-specific analyses indicated that plurality and nulliparity were associated with increased risk of metopic craniosynostosis and that macrosomia was associated with coronal craniosynostosis (Table IV). Of note, low birth weight was associated with risk of metopic craniosynostosis, and preterm delivery was associated with sagittal and metopic craniosynostosis. There were too few cases of lambdoidal or multiple suture synostosis to separately assess risks for constraint-related factors. Adjusted ORs for twins or higher order births after excluding mothers who had fertility treatments or procedures were 1.5 (95% CI 0.9–2.7) overall, 2.1 (95% CI 1.1–4.0) for sagittal cases and 1.8 (95% CI 0.5–5.9) for metopic cases. Of note, after this exclusion, all coronal cases were of singleton gestation; thus, no additional OR was calculated for this group. Of 65 infants in whom craniosynostosis was associated with other structural defects, only 6 had defects that have been associated with intrauterine constraint [Graham 2007]. These included 2 with hip dislocation with associated malformations (cleft lip and palate in one and diaphragmatic hernia in the other), 3 with talipes equinovarus with craniosynostosis (2 sagittal cases and one metopic case), and one infant with metopic craniosynostosis, who had a unilateral nonfunctioning kidney, bilateral hydronephrosis, and arytenoid hypertrophy. The remaining 59 infants with craniosynostosis and associated defects had defects that would be expected to occur early in pregnancy. Furthermore, when analyses were performed excluding infants with craniosynostosis and associated defects, or infants with a family history of craniosynostosis, results were similar to those for all infants with craniosynostosis.

DISCUSSION

Although no constraint-related factor had a large overall influence on craniosynostosis and some data were too sparse to allow for a well grounded scientific inference, our study found that plurality and nulliparity were both associated with a two fold increased risk for metopic craniosynostosis, plurality was associated with sagittal synostosis only when including cases with fertility treatments, and macrosomia had almost twice the risk of developing coronal craniosynostosis. Contrary to our hypothesis, prematurity and low birth weight were associated with craniosynostosis, rather than macrosomia and post-term gestation. Although the 4 hypothesized constraint-related factors were not associated with craniosynostosis when all suture types were combined, some types of craniosynostosis were associated with individual constraint-related factors.

Approximately 8% of all craniosynostosis cases are familial, with such cases usually transmitted as an autosomal dominant trait with incomplete penetrance and variable expressivity. Familial types account for 14.4% of coronal synostosis, 6% of sagittal synostosis, and 5.6% of metopic synostosis, while lambdoidal synostosis is almost never familial [Lajeunie et al., 2005]. The lower prevalence of familial cases for sagittal, metopic and lambdoidal synostosis, when compared with coronal synostosis may suggest a greater environmental influence.

Published results have been mixed regarding associations between constraint-related factors and nonsyndromic craniosynostosis [Alderman et al., 1988; Boulet et al., 2008; Reefhuis et al., 2003; Singer et al., 1999]. A study by Alderman et al. of 173 children with craniosynostosis and 759 control infants showed an association between multiple gestation and craniosynostosis (OR 3.0, 95% CI 1.2–7.1), but no association with parity [Alderman et al., 1988]. A study from Western Australia of 170 case infants and 522 control infants examined constraint-related factors including prolonged gestation >42 weeks, plurality, and

macrosomia, and none of these were significantly associated with craniosynostosis [Singer et al., 1999]. Similar to our findings, these investigators found an association between preterm delivery (< 37 weeks) and craniosynostosis (OR 2.9; 95% CI 1.8, 4.8) [Singer et al., 1999]. Källén et al. conducted an investigation using Swedish health registries and found an association with high parity (of 4 or more) (OR 1.7; 95% CI 1.2–2.4) for all forms of craniosynostosis, but no significant linear trend except for sagittal synostosis (p for linear trend = 0.01). Reefhuis et al found no association between multiple births nor primigravidity and craniosynostosis [Reefhuis et al., 2003]. Most recently Boulet et al. showed an increased prevalence of craniosynostosis among multiple births and infants with a birth weight >4000g [Boulet et al., 2008].

We found that the association of craniosynostosis with constraint-related factors varied by suture type and that these covariates were difficult to disentangle, despite having access to a large number of subjects. Fertility treatments and plurality are strongly associated with each other [Aston et al., 2008; Hoekstra et al., 2008], and fertility treatments may be associated with craniosynostosis [Reefhuis et al., 2003]. When we excluded subjects with fertility treatments, however, results for plurality were essentially unchanged for all suture types.

Gestational age and size at birth are highly correlated with each other and for analytic completeness our study and others have assessed the opposite ends of each factor. For low birth weight, it is important to distinguish between intrauterine growth restriction, which often demonstrates catch-up growth, and fetal growth deficiency, where typically no catch-up growth occurs. Fetal growth deficiency that continues after birth is associated with numerous syndromes and other problems [Rimoin and Graham 1989; Snijders et al., 1993]. It is possible that one of the many risk factors for prematurity is fetal constraint, yet based on the available dataset, we cannot determine the impact of fetal constraint on preterm delivery. Longitudinal studies have demonstrated evidence that constrained infants from multiple births are commonly born preterm with a low birth weight and typically show prompt postnatal catch-up growth [Dubois et al., 2007; Ijzerman et al., 2001; van Dommelen et al., 2008], and this has also been shown for infants with late fetal growth restriction [Harvey et al., 1979].

On the opposite end of the spectrum, post-maturity or prolonged gestation is associated with large for gestational infants [Chervenak 1992] and has a higher incidence of birth complications [Shea et al., 1998]. Although our study did not demonstrate evidence for an association between prolonged gestation and craniosynostosis, prolonged gestation has been associated with craniosynostosis in an animal model. In a murine study where fetal constraint was generated using a cervical clip and by delaying birth by 2–3 days, 88% of the 26 treated pregnant mice had evidence of craniosynostosis [Koskinen-Moffett 1986]. However, not all animal studies demonstrate such a strong association with craniosynostosis. Some hypothesize that a murine model is not an ideal system to study constraint, given that multiple gestation pregnancies are typical and the gestational period results in the birth of offspring that are significantly less developed.

Although low birth weight and early gestational delivery were not part of our proposed proxies for fetal constraint, both were assessed and found to be associated with the risk of developing craniosynostosis. Although speculative, it is possible that late gestational constraint could lead to early delivery of a fetus that is small in size due to premature delivery. Because of a consistent relationship between craniosynostosis and low birth weight/preterm delivery, factors involving preterm labor and delivery should be explored in more detail. Size at birth may potentially be more influenced by maternal size than by the intrinsic growth determinants of the fetus [Brooks et al., 1995; Drooger et al., 2005]. Many factors contribute to the occurrence of low birth weight, including genetic and

environmental factors such as parity, pregnancy spacing, maternal age and size, blood pressure, race, health, smoking, alcohol intake, twinning and intrauterine constraint [Cogswell and Yip 1995; Drooger et al., 2005; Opitz et al., 1985]. The influence of fetal constraint on size at birth has been studied in animal models, with the best example from 1938 where Walton and Hammond bred Shire horses (large) with the much smaller Shetland ponies and varied only the maternal breed (size). Birth weight correlated with maternal breed and size [Walton A. and Hammond J. 1938]. This suggests that late-gestational growth restriction due to small maternal size is compensated by rapid postnatal catch-up growth. Human studies reported similar observations for babies born after ovum donation, and their size at birth correlated more strongly with the ovum recipients than the ovum donors with respect to birth weight [Brooks et al., 1995]. It would be of interest to know in this cohort if low birth weight/preterm delivery is more common among fetuses delivered to short-statured mothers with tall partners, and whether or not such fetuses show prompt postnatal catch-up growth, as is frequently seen with multiple gestation infants carried to near term.

As has been documented in other studies of craniosynostosis, [Boulet et al., 2008; Singer et al., 1999], we also noted a male and non-Hispanic white predominance among the cases, compared to controls. Both of these variables could be associated with larger head size at birth, and this might suggest a role for fetal head constraint [Madan et al., 2002]. The association between macrosomia and pre-existing maternal diabetes is well accepted [Spellacy et al., 1985]. Because pre-existing diabetes is also associated with an increased risk for malformations, this factor was considered to be a criterion for exclusion of both cases and controls, even though isolated craniosynostosis is not a diabetes-related malformation [Correa et al., 2008]. Although we used an accepted definition of macrosomia (birth weight >4000g) as a surrogate for (unmeasured) large size in late gestational development, it is still unclear when in gestation premature suture fusion occurs, thus making it difficult to define the window of fetal development when the calvarial sutures are influenced by teratogens or the influences of size on fetal head constraint.

As the largest population-based study completed to date, our study had several strengths in assessing these four constraint-related factors. Not only were we able to assess an appropriate control population, we also have the statistical power to adjust for the available confounders. Also, all cases were clearly identified and reviewed by a clinical geneticist to ensure the study's inclusion criteria were met. However, our study also had several limitations. Attempts were made to exclude infants with craniosynostosis of known etiology (e.g., single-gene disorders and chromosome abnormalities) through careful review of information abstracted from medical records. However, infants mildly affected with these conditions and infants with Muenke syndrome were quite likely to have been inappropriately included, since molecular testing was not routinely performed on these infants. If molecular testing was pursued clinically and found to be abnormal, then these infants were excluded from the study. We assumed that syndromic cases might be more frequent among infants with coronal involvement; thus we analyzed infants with sagittal, metopic and coronal involvement separately. There were too few infants of multiple sutural involvement or lambdoid involvement to perform a meaningful analysis, so these groups were not analyzed separately from infants with either sagittal, coronal or metopic involvement.

We acknowledge that although multiple gestation, macrosomia, post dates, and nulliparity are relatively easy to ascertain using a maternal questionnaire and though they are good measures of general constraint, they may not reflect fetal head constraint, which is the issue in question. The four factors we chose are either poor proxies for fetal head constraint or not major factors in the overall cause of non-syndromic craniosynostosis, which is likely a

multifactorial defect of heterogeneous etiology. Yet these were the variables available in this very large dataset that systematically ascertained data using one of the most comprehensive questionnaires administered to both case and control mothers. Another limitation is that the NBDPS does not routinely ascertain information on *in utero* positioning or amniotic fluid status (e.g., oligohydramnios) across all sites. The risk of recall bias, for example, relying on parental recall of use of fertility treatment instead of abstracting data from all medical records, was another weakness. Also, information was collected by telephone several months after delivery and the interval between delivery and phone interview was different between the cases and controls. Although fetal head constraint cannot be directly measured, we were unable to study constraint-related factors that had been previously reported in case studies of non-syndromic craniosynostosis. These unavailable and therefore unstudied factors included the sensation of early descent of the fetal head into the lower uterine segment [Graham et al., 1979], abnormal birth presentation which has an increased rate of preterm birth [Higginbottom et al., 1980], and the presence of uterine malformations which may also be associated with preterm birth, malpresentation and craniosynostosis [Graham and Smith 1980]. Such factors could potentially limit fetal movement and cause fetal constraint. We could not evaluate whether combinations of factors leading to fetal head constraint might have synergistic effects that increase the risk of craniosynostosis. And finally, it was unfortunate that this study had no postnatal follow-up data to determine whether or not fetuses that delivered early with low birth weight ultimately caught up in growth, which might suggest they delivered early because of fetal constraint in late gestation.

Although uncertainties remain regarding the influence of fetal head constraint, we conclude that no single constraint-related factor assessed in this study contributed greatly to the risk of craniosynostosis. Here we have demonstrated some evidence of suture-specific environmental influences, but these constraint-related factors and others will need further investigation in order to increase our understanding of the underlying causes of craniosynostosis.

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TABLE I

Characteristics of Infants with Craniosynostosis (Cases) and Infants with No Major Birth Defects (Controls), the National Birth Defects Prevention Study, 1997–2004.

Characteristics	Cases (n=670)	Controls (n=5,928)
Infant sex		
Male	66.1% (443)	50.3% (2982)
Female	33.9% (227)	49.6% (2941)
Maternal education (years)		
Less than 12	11.2%(75)	16.6% (986)
12	23.7%(159)	24.7%(1464)
More than 12	63.6%(426)	57.2% (3389)
Maternal race or ethnicity		
Non-Hispanic white	74.2%(497)	59.5% (3524)
Non-Hispanic African American	4.6% (31)	11.4%(674)
Hispanic	16.0%(107)	22.3% (1323)
Asian or Pacific Islander	1.8% (12)	3.0% (175)
Native American/Alaskan native	0.5% (3)	0.5% (27)
Other	2.8% (19)	3.1% (183)

TABLE II

Type of Craniosynostosis Among Case Infants in the National Birth Defects Prevention Study, 1997–2004

Characteristics	Number	(%)
Type of Suture involved		
Sagittal	357	(53.3%)
Metopic	116	(17.3%)
Coronal	113	(16.9%)
Lambdoidal	23	(3.4%)
Multiple	59	(8.8%)
Unknown	2	(0.3%)
Infant Classification		
Isolated*	605	(90.3%)
Multiple§	65	(9.7%)

*Infants with no other unrelated major birth defects.

§Infants with one or more unrelated major birth defects.

TABLE III

Summary of constraint-related factors for all suture types combined, the National Birth Defects Prevention Study, 1997–2004.*

Characteristics	No. Cases	No. Controls	OR(95% CI) Crude	No. Cases	No. Controls	OR(95% CI) Adjusted‡
Plurality						
Singleton	637	5,726	Reference	592	4950	Reference
Twin or higher order	32	141	2.0 (1.4–3.0)	29	125	1.4 (0.9–2.3)
Birth weight						
Low Birth weight	45	269	1.7 (1.2–2.3)	41	227	1.9 (1.3–2.7)
Normal weight	485	4,882	Reference	450	4221	Reference
Macrosomia	88	613	1.4 (1.1–1.8)	82	535	1.1 (0.9–1.5)
Gestational Age						
Preterm	84	470	1.7 (1.3–2.2)	80	399	1.9 (1.5–2.5)
Term	542	5,210	Reference	504	4518	Reference
Prolonged	12	106	1.1 (0.6–2.0)	9	83	1.0 (0.5–2.1)
Parity						
No prior birth	230	2,302	0.9 (0.7–1.1)	210	1988	1.0 (0.8–1.3)
One	229	1,947	1.0 (0.8–1.3)	214	1690	1.1 (0.9–1.3)
2 or more	176	1,520	Reference	168	1321	Reference

*All analyses excluded mothers with pre-pregnancy diabetes and all analyses except those of plurality also excluded multiple births.

‡All adjusted models included maternal body mass index, education, race-ethnicity, age, fertility treatments, infant sex, gestational diabetes and smoking.

TABLE IV

Summary of constraint-related factors by affected sutures, the National Birth Defects Prevention Study, 1997–2004 *

Characteristics	No. Controls	No. Cases	Sagittal Adjusted OR (95% CI)	No. Cases	Metopic Adjusted OR (95% CI)	No. Cases	Coronal Adjusted OR (95% CI)
Plurality							
Singleton	4950	313	Reference	98	Reference	104	Reference
Twin or higher order	125	16	1.6 (0.9–2.9)‡	8	2.2 (1.0–4.9)‡	3	0.7 (0.2–2.3)‡
Birth weight							
Low birth weight	227	16	1.5 (0.9–2.5)	13	3.6 (1.9–6.7)	6	1.7 (0.7–3.9)
Normal weight	4221	246	Reference	73	Reference	72	Reference
Macrosomia	535	42	1.0 (0.7–1.4)	12	1.0 (0.5–1.9)	19	2.0 (1.2–3.4)
Gestational Age							
Preterm	399	37	1.7 (1.2–2.5)	18	2.8 (1.6–4.7)	9	1.1 (0.5–2.2)
Term	4518	269	Reference	79	Reference	95	Reference
Prolonged	83	7	1.5 (0.7–3.4)	1	--	0	--
Parity							
No prior birth	1988	101	0.9 (0.6–1.2)	47	2.0 (1.1–3.7)	33	0.8 (0.5–1.3)
One	1690	118	1.0 (0.8–1.4)	33	1.5 (0.8–2.8)	33	0.8 (0.5–1.3)
2 or more	1321	93	Reference	18	Reference	38	Reference

*All analyses excluded mothers with pre-pregnancy diabetes and all analyses except those of plurality also excluded multiple births; odds ratios were calculated only if all cells had at least two observations.

‡All adjusted models included maternal body mass index, education, race-ethnicity, age, fertility treatments, infant sex, gestational diabetes and smoking.