

Original article

In utero and perinatal complications preceding asthma

Background: It has been suggested that pregnancy and early life may influence the development of asthma in the offspring, but published studies have not carefully controlled for potential biases.

Methods: In a large British birth cohort of 4065 natural children of 2583 mothers, we investigated whether *in utero* and perinatal influences contribute to the development and the severity of asthma in childhood, allowing for possible confounders of the relationship, and considering the nonindependence of familial data.

Results: Child asthma (10.1%) was more frequently reported by mothers when there had been health complications during pregnancy (prevalence = 14.3%; adjusted odds ratio [OR_{adj}] = 2.01; 95% confidence interval, 1.52–2.67), labor, or delivery (19.3%, OR_{adj} = 1.35, 1.01–1.81); child illness or health complications during the first week of life (22.6%, OR_{adj} = 1.35, 1.01–1.82); and birth weight of <2.5 kg (7.0%, OR_{adj} = 1.57, 1.10–2.25). Specific causes of health complications during pregnancy which significantly related to asthma were early or threatened labor (ICD: 644) (4.8%, OR_{adj} = 1.58, 1.03–2.40) and the malposition or malpresentation of the fetus (ICD: 652) (1.6%, OR_{adj} = 3.63, 1.47–8.91).

Conclusions: The results provide further evidence that *in utero* and perinatal factors may increase the risk of developing asthma.

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Bronchial asthma is one of the most common medical problems complicating pregnancy (1, 2), and both the effect of pregnancy on the course of maternal asthma (3) and the effect of maternal asthma on the course of pregnancy (1) have been documented (4, 5). Previous studies have suggested that, in addition to genetic liability and environment in early childhood, intra-uterine life also influences the development of asthma beyond childhood. Small babies, prematurity, young maternal age, and maternal smoking have all shown an association with asthma in the offspring (6–10), probably because they result in lower birth weight and reduced lung function. Furthermore, gestational age and high birth length increased the risk of asthma also in adulthood, supporting the hypothesis that, among other factors, poor intrauterine growth is involved in the multifactorial etiology of asthma (11). However, the studies which have found such links were restricted from the methodological point of view, as the populations were often inadequate, the number of considered factors was insufficient, and potential biases were not controlled for. This paper presents findings from a national British cohort and their offspring to investigate whether various *in utero* and perinatal influences contribute to the development and the severity of asthma in childhood. With this end, the relationship was adjusted for possible confounders, namely, the factors predisposing to either

health complications in pregnancy or child asthma, and the nonindependence of data among siblings was taken into account in the statistical analysis.

Material and methods

The National Child Development Study (NCDS) and the study design

All persons born in the UK during the week 3–9 March 1958 and subsequent immigrants of the same dates of birth have been followed periodically through childhood into adult life in the National Child Development Study (NCDS). At the latest follow-up in 1991 (at age 33 years), 5765 women and 5580 men were interviewed, and 7750 had at least one surviving child. The entire households of a random 1/3 sample of these 7750 cohort members (CMs) were invited to participate in an extended interview including questions relating to the health of the mothers (including the partners of male CMs) and all their children. Trained nurses administered interviews especially designed to record health events in detail. Detailed methods and the randomization process were described elsewhere (12). Data on the mothers included medical history during pregnancy, labor, and delivery, as well as potential risk factors during the course of the pregnancy. Data on the children comprised prematurity, birth weight, breast-feeding, and illness or health complications during the first week of life, as well as history of asthma. From the NCDS records, history of asthma, smoking habits, family composition and socioeconomic status (SES) of each CM were also obtained. Each CM was assigned to one of the following four socioeconomic classes: managers, clerks, skilled manual workers, and unskilled manual workers.

Definition of variables

Antenatal outcome variables included maternal health complications which had needed medical supervision apart from routine checks and hospital admissions at any time during pregnancy before labor began, as well as amniocentesis, exposure to ultrasound scan, and pelvic radiography. Perinatal outcomes comprised induced labor, maternal health complications during labor and delivery, sedatives or painkiller intake (entonox, epidural, pethidine, and general anesthesia), type of delivery (natural, forceps, cesarean section, and ventouse), gestational age, breast-feeding, child birth weight, malformations at birth, and health complications during the first week of life. The *International Classification of Diseases, 9th Revision (ICD-9)*, was used to record information about health complications, hospital admissions, and malformations. Prematurity (gestational age ≤ 36 weeks) and birth weight of < 2.5 kg were used in the analysis.

Asthma in the children was ascertained with the standardized questions shown in Table 1. The age of onset of asthma was also recorded. Severe asthma in the past year was defined on the basis of persistent attacks (more than 12 in the last 12 months) associated with attacks severe enough to limit speech to only one or two words at a time between breaths, and ever being woken at night by an attack, as proposed in the International Study of Asthma and Allergies in Children (13). Potential factors associated with both child asthma and the antenatal or perinatal factor considered (confounders in the study of the relationship between pregnancy events and child asthma all factors) were as follows:

- 1) age, sex, prematurity, birth weight of < 2.5 kg, sibship size, and birth order with regard to the child
- 2) age at child's birth, parity (primipara vs other), smoking during the 12 months before child was born (*in utero* smoking), and asthma with regard to the mother.

Self-reporting of *in utero* smoking has been shown to be highly related to maternal urine cotinine during pregnancy (14). In addition, the CM's history of active smoking was considered a marker of parental smoking at the time of the survey in the whole sample, and as measurement of maternal active smoking at the survey in the subsample obtained after exclusion of the male CMs. Birth order and sibship size were discarded in the adjusted models because of their collinearity with maternal parity.

Statistical analysis

The percentages were compared with the χ^2 test, and the means of different groups with the analysis of variance. The odds ratio adjusted simultaneously for confounders was used as a measure of the association between child asthma and risk factors, and it was calculated by the logistic regression model under the assumption that measures among siblings were not independent. By relation of the binary response (asthma [yes, no]) of each child of the family to risk factors (*in utero* and perinatal factors) and confounders, the model took possible correlations among binary responses into account and provided a consistent robust variance estimate of the estimated regression parameters necessary to compute the adjusted odds ratio (15). Goodness-of-fit statistics for all models relative to residuals against predicted values did not indicate any evidence of lack of fit. The graphical method based on the analysis of the plot was used to this extent.

Results

Characteristics of sample

The random sample of one in three families included 2583 mothers (1522 CMs and 1061 partners of male CMs). Mean age among the mothers who were not CMs was

31.0 ± 3.3 years. There were no meaningful differences between CMs who had participated and those who had not with respect to age of the children, sex, familial status, or SE class. The total sample included 4153 natural children (49.8% males), aged between 1 year and 18 years; but, of those, 4065 had full details on asthma and antenatal and perinatal risk factors. Information on specific causes of maternal and child hospital admissions and health problems was not available for 482 children. There were no differences between children for whom specific causes were known and those whose age, sex, and SES were not known. Among the initial 4153 children, first-parity births accounted for 60% of the total births, and there were 1339 only children (i.e., with no siblings). The number of twin pairs was trivial in the cohort, and twinning was not taken into account in the analysis.

As expected, asthma was more common in boys than in girls (12.2% vs 8.2%; $P = 0.001$) and depended on age (Table 1). Both parental asthma and parental smoking were significantly related to child asthma (17.8% in asthmatic children vs 8.0% in others; $P < 0.001$; 39.2% in asthmatics vs 33.3% in others; $P = 0.02$, respectively). Conversely, *in utero* exposure to smoking was not significantly associated with child asthma in this population (38.8% in asthmatics vs 35.6% in others; NS).

Relationships to antenatal and perinatal factors

The prevalence of maternal health complications and hospital admission during pregnancy, and maternal health complications during labor or delivery increased significantly ($P < 0.10$) with parental asthma and smoking as well as with *in utero* exposure to smoking. *In utero* exposure to smoking was also positively related, as expected, to prematurity and birth weight of < 2.5 kg, and inversely related to breast-feeding (Table 2). Furthermore, maternal health complications and hospital admission during pregnancy, maternal health complications during labor or delivery, emergency cesarean, birth weight of < 2.5 kg, and child illness or health complications in the first week of life were significantly associated with asthma in the offspring (Table 3). Adjustment for confounders did not modify the association with maternal health complications during pregnancy, labor, or delivery; birth weight of < 2.5 kg; and child illness or health complications in the first week of life (Table 3). Stratifying the sample according to whether the mother was a CM or not in order to avoid response bias yielded similar results. Actually, higher odds ratios were observed in the subsample of female CMs in the case of maternal health complications during pregnancy, maternal health complications during labor or delivery, child illness or health complications in the first week of life, and birth weight of < 2.5 kg (Table 3). Similarly, considering the samples of first-parity offspring and only children, respectively, in order to control for confounding effects (genetic and environmental) that

Table 1. Percentage prevalence of child asthma symptoms by age

	All (n=4153)	0–3 years (n=1146)	4–6 years (n=1091)	7–9 years (n=925)	10–18 years (n=991)	P*
Asthma, % (Has your child ever had attacks of ...?)	10.1	6.4	10.5	12.3	11.8	0.001
Last attack						
<1 month, %	19.3	31.3	15.6	14.5	17.3	0.001
1–12 month(s), %	42.9	52.0	49.5	39.0	31.8	
>12 months, %	37.8	16.7	35.0	46.5	50.8	
	15.6	14.5	17.3			
	49.5	39.0	31.8			
	35.0	46.5	50.8	0.001		
Number of attacks in past year						
1–3, %	73.6	78.1	76.9	68.7	67.4	NS
4–12, %	20.1	18.7	18.2	22.9	22.1	
>12, %	6.3	3.3	5.0	8.4	10.5	
Ever woken at night, % (Has he/she ever been woken at night by an attack?)	53.0	51.3	57.7	51.9	50.5	NS
Last attack of waking at night						
<1 month, %	18.4	29.3	18.8	14.3	13.0	0.001
1–12 month(s), %	42.3	53.7	48.2	37.4	31.0	
>12 months, %	39.2	17.1	33.0	48.4	56.0	
Ever difficult speech, % (Has an attack ever been bad enough to limit speech to only one or two words at a time between breaths?)	22.7	13.6	24.9	24.7	26.3	0.024
Last attack of difficult speech						
<1 month, %	10.6	26.9	3.6	8.5	11.8	0.001
1–12 month(s), %	35.2	61.5	36.4	31.9	23.5	
>12 months, %	54.2	11.5	60.0	59.6	64.7	

*Comparison between classes of age.

may be introduced when using more than one child from a single family yielded similar results. Furthermore, the observed associations did not depend on the age of the onset of asthma. There was a significant increase in the

report of severe asthma in the past year according to maternal health complications, including hospital admission during pregnancy, labor, or delivery, as well as child's birth weight of <2.5 kg and illness or health

Table 2. Percentage prevalence of antenatal and perinatal risk factors in relation to parental asthmatic status and smoking

Factors	All (n=4065)	Parental asthma		Parental smoking		In utero exposure to smoking	
		Yes (n=370)	No	Yes (n=1386)	No	Yes (n=1442)	No
Antenatal outcomes							
Ultrasound scan, %	82.2	85.4	81.9	77.6	84.6†	78.9	84.1†
Pelvic radiography, %	3.7	4.3	3.6	3.8	3.6	3.6	3.7
Amniocentesis, %	5.2	6.8	5.1	5.3	5.2	5.3	5.2
Maternal health complications during pregnancy, %	14.3	18.9	13.9*	12.5	15.3*	13.3	14.9
Maternal hospital admission during pregnancy, %	28.5	32.7	28.0	31.4	27.0*	31.3	26.9*
Perinatal outcomes							
Induced labor, %	27.8	26.0	28.0	28.6	27.4	29.7	26.8
Type of delivery (compared to natural), %							
With forceps	14.5	14.4	14.5	13.6	14.9	13.9	14.8
By cesarean	4.0	5.2	3.9	3.6	4.3	3.0	4.6
By emergency cesarean	7.1	8.2	7.0	7.5	7.0	7.4	7.0
By another way	1.9	2.2	1.9	1.8	2.0	1.9	2.0
Sedative or painkiller intake during delivery (compared to nothing), %							
Entonox	57.6	50.3	58.4	54.6	59.2	55.9	58.6
Epidural	11.9	15.8	11.5	11.0	12.4	10.4	12.8
Pethidine/meptin	12.2	12.8	12.1	14.1	11.2	13.2	11.6
General anesthesia	5.3	7.1	5.1	6.0	4.9	6.7	4.5
Other	0.7	0.3	0.7*	0.8	0.6*	0.8	0.6*
Maternal health complications during labor or delivery, %	19.3	23.5	18.9*	18.2	19.9	19.5	19.3
Child illness or health problems in first week of life, %	22.6	25.7	22.3	22.7	22.6	22.7	22.6
Breast-feeding at all, %	65.4	63.8	65.5	54.3	71.1†	56.7	70.2†
Prematurity (≤36 weeks), %	9.8	12.3	9.6	9.9	9.8	11.3	9.0*
Birth weight <2.5 kg, %	7.0	8.2	6.9	7.6	6.7	8.7	6.0†

*P<0.05; †P=0.001.

Table 3. Relationships of antenatal and perinatal risk factors to child asthma

Factors	All children (n=4065)				Among children whose mother is cohort member (n=2420)	
	Crude OR*	(95% CI)†	Adjusted OR‡	(95% CI)	Adjusted OR‡	(95% CI)
Antenatal outcomes						
Ultrasound scan	0.99	(0.75, 1.30)				
Pelvic radiography	1.01	(0.59, 1.74)				
Amniocentesis	0.67	(0.38, 1.18)				
Maternal health complications during pregnancy	1.86	(1.44, 2.41)	2.01	(1.52, 2.67)	2.21	(1.55, 3.16)
Maternal hospital admission during pregnancy	1.30	(1.04, 1.62)	1.23	(0.98, 1.55)	1.15	(0.87, 1.52)
Perinatal outcomes						
Induced labor	1.13	(0.90, 1.41)				
Emergency cesarean	1.47	(1.02, 2.10)	1.20	(0.74, 1.97)	0.91	(0.44, 1.86)
General anesthesia at delivery	1.23	(0.77, 1.95)				
Maternal health complications during labor or delivery	1.44	(1.12, 1.85)	1.35	(1.01, 1.81)	1.36	(0.89, 2.07)
Child illness or health complications in first week of life	1.52	(1.21, 1.91)	1.35	(1.01, 1.82)	1.48	(1.02, 2.15)
Breast-feeding at all	0.93	(0.74, 1.16)				
Prematurity (≤ 36 weeks)	1.26	(0.90, 1.76)				
Birth weight < 2.5 kg	1.60	(1.12, 2.29)	1.57	(1.10, 2.25)	2.16	(1.43, 3.27)

*Odds ratio according to logistic regression model for correlated binary data (Ref. 14).

†95% confidence interval.

‡Odds ratio according to logistic regression model for correlated binary data adjusted for confounders.

complications in the first week of life, with mild asthma in an intermediate position compared to the absence of asthma (Table 4).

Analysis of specific complications of pregnancy and labor showed that, after adjustment for potential confounders, early or threatened labor (ICD: 644) (4.8%), and malposition and malpresentation of the fetus at birth (namely, breech, transverse lie, and face presentation) (652) (1.6%) conferred a significantly increased risk of asthma for the child (Fig. 1). No significant relationship was observed for specific causes of child illness in the first week of life.

Discussion

Several characteristics of pregnancy have already been reported to influence the likelihood of developing

childhood asthma (16, 17), namely, smoking exposure *in utero*, poor antenatal care, poor maternal weight gain during pregnancy, low maternal age, prematurity, birth weight of < 2.5 kg, high birth length, cesarean section, and the use of opioids in labor. Our data identified additional early-life factors, as the risk of asthma in children was associated with maternal health complications during pregnancy, labor, and delivery, as well as neonatal illness and health complication in the first week of life. In particular, the risk increased with early and threatened labor and malpresentation and malposition of the fetus. The results were strengthened by the fact that such factors were also related to child asthma severity.

In order to assess the independent role of early-life factors in the expression of asthma, we adjusted for factors that could predispose to either child asthma or

Table 4. Percentage prevalence of antenatal and perinatal factors in relation to asthma severity

Factors	No asthma	Mild asthma (n=392)	Severe asthma (n=14)	P*	Crude OR† between mild and no asthma	Crude OR between severe and no asthma
Antenatal outcomes						
Ultrasound scan, %	82.2	81.9	85.7		0.98 (0.75, 1.28)	1.34 (0.29, 5.81)
Pelvic radiography, %	3.7	3.3	14.3		0.90 (0.51, 1.61)	4.38 (0.97, 19.78)
Amniocentesis, %	5.4	3.8	0		0.70 (0.41, 1.19)	0.60 (0.04, 10.12)
Maternal health complications during pregnancy, %	13.4	22.5	21.4	0.001	1.87 (1.45, 2.41)	1.76 (0.49, 6.33)
Maternal hospital admission during pregnancy, %	27.9	33.2	42.9	0.04	1.28 (1.03, 1.60)	1.94 (0.67, 5.60)
Perinatal outcomes						
Induced labor, %	27.6	29.6	42.9		1.10 (0.88, 1.39)	1.97 (0.70, 5.69)
Emergency cesarean, %	6.8	10.0	0		1.53 (1.07, 2.18)	0.64 (0.04, 10.81)
General anesthesia during birth, %	5.1	6.4	0		1.27 (0.83, 1.96)	1.31 (0.17, 10.03)
Maternal health complications during labor or delivery, %	18.7	24.5	35.7	0.007	1.41 (1.10, 1.80)	2.41 (0.81, 7.22)
Child illness or health complication in first week of life, %	21.8	29.6	35.7	0.001	1.51 (1.20, 1.90)	1.99 (0.67, 5.96)
Breast-feeding at all, %	65.5	63.5	71.4		0.92 (0.74, 1.14)	1.32 (0.41, 4.20)
Prematurity (≤ 36 weeks), %	9.6	11.9	7.1		1.28 (0.92, 1.78)	0.72 (0.09, 5.55)
Birth weight < 2.5 kg, %	6.6	10.1	14.3	0.025	1.58 (1.10, 2.26)	2.35 (0.52, 10.57)

*Global comparison.

†Odds ratio.

Specific causes [9th ICD*]

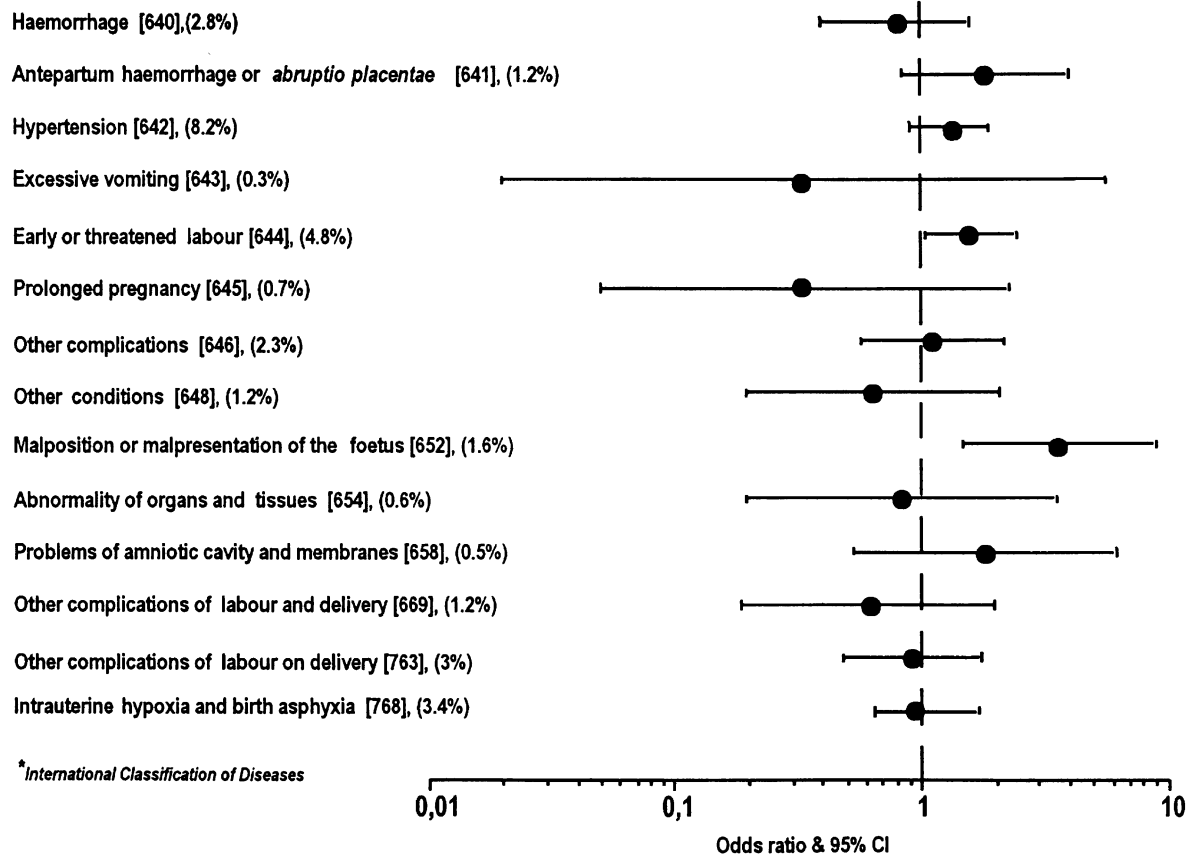


Figure 1. Relationships of specific causes of maternal health complications during pregnancy, labor, and delivery to child asthma (odds ratio and 95% confidence interval).

health complications in pregnancy, labor, and delivery. Indeed, studies which examined the outcome of pregnancy in asthmatic women have indicated that maternal asthma, which is highly related to child asthma, could predispose mothers to premature labor (1, 8), to increased frequencies of cesarean delivery (19), and to low-birth-weight infants (20), even if most of these studies have been poorly controlled for asthma therapy and other confounders. Similarly, maternal smoking is responsible for preterm delivery, low birth weight, and child asthma, but the results are still controversial in some cases (21). In addition, other factors such as maternal age at birth, primiparity, and low birth weight might also influence the relationships between antenatal and perinatal factors and asthma in the offspring (17). Our study was well placed to control confounding due to the availability of histories of asthma and smoking in the parents as well as detailed assessment of antenatal and perinatal circumstances. The results were adjusted for child prematurity, suggesting that health complications during pregnancy, labor, and delivery, as well as neonatal illness and health complication in the first week of life, might be primary etiologic factors for asthma rather than markers of prematurity. It seemed inappropriate to control in fine

detail for birth weight in our analysis. Actually, the issue concerning the adjustment for low birth weight at birth is complicated, as it has been suggested that birth weight is not a confounding variable, but an intermediate factor, because it may be a consequence of obstetric complications.

Some alternative explanations for the observed associations could not be completely eliminated in our study. We controlled for a broad range of potential confounders, but not for medication used during pregnancy or overall in asthmatic mothers. However, although chronic systemic steroid use has been associated with a slight increase in premature deliveries and low-birth-weight infants, these effects are minimal when weighed against the rare event of the effects of maternal hypoxemia (8) on the fetus because of uncontrolled asthma. Similarly, β -mimetics, which are given to mothers to stop premature labor, have been implicated in long-term effects in children (22), but without confirmation by population-based data. Furthermore, the factors we identified were consistently related to asthma also in the group of children without a family history of asthma.

Although our analysis relied upon retrospective ascertainment of antenatal and perinatal events, it has

been shown that the best reliability and validity in recollection when using administered questionnaires is obtained in the case of medical complications during pregnancy, labor, or delivery (23). There were few mothers in our population for whom recall could have been particularly difficult because of the age of the child or multiple pregnancies. Furthermore, trained nurses who ascertained their existence recorded health events. Recall bias might also have arisen because parents of asthmatic children might have been better at recalling both pregnancy complications and episodes of asthma than parents of nonasthmatic children. However, episodes of respiratory outcomes rather than complications of pregnancy would be more likely to be remembered by this group, since there was no evidence at the period of the survey that pregnancy was detrimental to asthma in the offspring; therefore, the relationships would have been underestimated. No distinction could be made between “transient” and “persistent” wheezing, as only ever having asthma was available in the analysis. However, this seemed meaningless in our context, as “transient” wheezing has not been related to late childhood or adult asthma (24). The effects of pregnancy characteristics on child asthma persisted independently of the age of the child, as all the models took child age into account. Lastly, findings for all children were not biased by the fact that some mothers did not belong to the cohort since they persisted in the group of children whose father was a CM.

It is becoming increasingly apparent that long-term immune and pulmonary systems are programmed already during intrauterine life, although the precise mechanisms are unknown (25). It is likely that a complex interaction of perturbed cytokine levels at the maternofetal interface with genotype and *ex utero* events dictates whether clinically significant asthma manifests itself in the child and, later, the adult (26). Inflammation, the primary component of any allergic process, might be the result of the exposure of the fetus to the mediators released across or from the placenta during fetal life due to allergen exposure *in utero* (27). However, it has also been suggested that allergic inflammation might result from other intrauterine factors, as both raised cord-blood IgE levels and asthma in childhood have been associated with increased head circumference at birth (28, 29), which depends on nutritional factors during fetal life, either undernutrition (28), because of brain-sparing strategy

(30), or overnutrition (28). Population-based studies have consistently shown that babies who are small or disproportionate at birth, or who have altered placental growth, also have increased rates of cardiovascular disease, stroke, and diabetes in adult life. Alternatively, other unidentified antenatal and perinatal processes might contribute to fetal lung or airways injury and thus to respiratory illness in childhood in susceptible individuals (31, 32). Observed associations might result from fetal “programming”, whereby a stimulus or insult at a critical, sensitive period of early life might have permanent effects on the body’s structure, physiology, and metabolism. Persisting changes in the level of hormone secretion and tissue sensitivity may link fetal factors with adult disease. Such data are consistent with our results showing that unidentified processes responsible for or associated with health complications during pregnancy, labor, or delivery; child illnesses; or health complications during the first week of life are related to asthma. Lastly, it cannot be excluded that *in utero* processes can act as stressors contributing to a change in the maturation of the autonomic nervous system involved in the control of respiration through the innervation of smooth muscles (3). Nevertheless, there is little evidence to support such a hypothesis.

These findings among the offspring of a nationally representative birth cohort obtained after controlling for potential confounders provide further epidemiologic evidence that the risk of developing childhood asthma may be influenced to some extent by events in pregnancy or delivery. Confirmatory studies to define how genetic and early life factors interact in the developing lung and lead to the onset of asthma, and more detailed investigation of specific antenatal and perinatal complications are required.

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