Mode of Delivery and Asthma at School Age in 9 European Birth Cohorts

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Evidence on the association between mode of delivery and asthma at school age is inconclusive. We assessed the associations between specific modes of delivery and asthma in children from 9 European birth cohorts that en-rolled participants between 1996 and 2006. Cohort-specific crude and adjusted risk ratios for asthma at ages 5–9 years were calculated using Poisson regression models and pooled. A sensitivity analysis was carried out in chil-dren born at term to reduce confounding due to perinatal factors. The study included 67,613 participants. Cohort-specific rates of cesarean delivery varied from 9.4% to 37.5%. Cesarean delivery, as opposed to vaginal delivery, was associated with an increased risk of asthma (adjusted risk ratio (aRR) = 1.22, 95% confidence interval (CI): 1.02, 1.46). Compared with spontaneous vaginal delivery, the adjusted risk ratio was 1.33 (95% CI: 1.02, 1.75) for elective cesarean delivery, 1.07 (95% CI: 0.94, 1.22) for emergency cesarean delivery, and 0.97 (95% CI: 0.84, 1.12) for operative vaginal delivery. In children born at term, the associations were strengthened only for elective cesarean delivery (aRR = 1.49, 95% CI: 1.13, 1.97). The large sample size allowed analysis of the associations between specific modes of delivery and asthma at school age. The increased risk of asthma associated with elec-tive cesarean delivery, especially among children born at term, is relevant in counteracting the increasing use of this procedure, which is often performed without a clear medical indication.

Abbreviations: aRR, adjusted risk ratio; CHICOS, Developing a Child Cohort Research Strategy for Europe; CI, confidence interval; DNBC, Danish National Birth Cohort; EDEN, Etude des Déterminants pré et post natals du Développement et de la Santé de l'Enfant; GASPII, Genetica e Ambiente: Studio Prospettico sull'Infanzia in Italia; INMA, Infancia y Medio Ambiente (Environment and Childhood) Project; KOALA, Child, Parents and Health: Lifestyle and Genetic Constitution; OR, odds ratio.

There is increasing evidence that aspects of the prenatal and perinatal environment are involved in the etiology of several chronic disorders, including respiratory disorders (1). In 2 meta-analyses published in 2007 and 2008, investigators found a 20% increased risk of asthma among children deliv-ered by cesarean section (2, 3). More recently, other studies, based on prospective birth cohorts or registers linking asth-ma risk to cesarean delivery, have found inconsistent re-sults: Cesarean delivery has been found to be associated, not associated, or associated only in selected populations (such as allergic mothers) with wheezing or asthma in chil-dren (4–12). Only a few of these studies could distinguish be-tween different modes of delivery (4, 7–9, 11, 12), again with inconsistent results between emergency and elective cesarean section. Some of these inconsistencies might also arise from difficulties in controlling for confounding, especially for complications in pregnancy, and perinatal factors. There is much less information on the risk of asthma associated with other obstetrical interventions leading to vaginal delivery; in a recent study on forceps delivery, Hancox et al. (13) found
an association which weakened after controlling for confounders.

As was underlined in a recent editorial (14), the issues of long-term associations of emergency and elective cesarean delivery with asthma or allergic diseases and whether a causal association between mode of delivery and these out-comes exists are still far from being resolved. The problem lies in the fact that there are many potential factors influen-cing the choice of mode of delivery, including prepreg-nancy, pregnancy, and perinatal medical factors, as well as preferences of the pregnant woman and clinical practice pat-terns (15).

The rate of cesarean delivery has continued to increase in low-, middle-, and high-income countries, largely exceeding the recommendations of the World Health Organization, which indicated that the procedure might be appropriate in up to 15% of deliveries (16). At least in high-income coun-tries, the increased rate is mainly due to a rise in elective ce-sarean delivery, often without a medical indication. It could therefore be of primary interest for clinicians to know whether elective cesarean delivery is associated with an in-creased risk of a widespread disease like asthma.

In the present study, we assessed the association be-tween mode of delivery and current asthma in school-age children, pooling individual data from several prospective European birth cohort studies participating in the CHICOS (Developing a Child Cohort Research Strategy for Europe) Project (http://chicosproject.eu/), to obtain robust results across heterogeneous settings and to achieve sufficient statistical power to disentangle the associations between different modes of delivery and asthma. We controlled for several potential confounders by adjustment, and we re-duced unmeasured confounding by restricting the analysis to infants born at term.

METHODS

Potential cohorts to be included were identified through the birth cohort inventories Birthcohorts.net (www.birthcohorts.net) (17) and Environmental Health Risks in European Birth Cohorts (http://www.enrieco.org/) (18) and through direct contact with researchers participating in the European CHICOS Project. Birth cohorts were eligible if en-rollment had started after 1990 and if the investigators pos-sessed suitable information on both mode of delivery and current asthma in children at early school age.

Cohorts that agreed to participate and met the inclusion criteria were: the Danish National Birth Cohort (DNBC) (Denmark) (19); l'Etude des Déterminants pré et post natals du Développement et de la Santé de l'Enfant (EDEN) (Nancy and Poitiers, France) (20); Genetica e Ambiente: Studio Prospettico sull'Infanzia in Italia (GASPII) (Rome, Italy) (21); the Generation R Study (Rotterdam, the Netherlands) (22); Generation XXI (Porto, Portugal) (23); the Infancia y Medio Ambiente (Environment and Childhood) Project (INMA) (Spain; Menorca site only) (24); Child, Par-ents and Health: Lifestyle and Genetic Constitution (KOALA) (the Netherlands) (25); Lifeways Cross-Generation Cohort Study (Lifeways) (Dublin and Galway, Ireland) (26); and the Southampton Women's Survey (Southampton, United King-dom) (27). Multiple births were excluded from the analysis, since mode of delivery and current asthma prevalence may differ between multiples and singletons.

All original cohort studies were approved by their local ethical committees, and investigators provided written in-formed consent to use their data.

Exposure and outcome assessment

Mode of delivery was classified as spontaneous vaginal, operative vaginal, elective cesarean, or emergency cesarean. The INMA Menorca and KOALA cohort investigators collected data on mode of delivery categorized only as vaginal or cesarean, without further specifications. For most cohorts, information on mode of delivery was ex-tracted from obstetrical records, while for the DNBC co-hort it was obtained through linkage with the National Hospital Discharge Registry, and for INMA Menorca and KOALA it was collected using maternal self-administered questionnaires.

For all of the cohorts, information on asthma and wheez-ing symptoms was obtained from a parental questionnaire filled in when the child was between the ages of 5 and 9 years. Current asthma was defined as ever occurrence of asthma and wheezing or whistling in the chest during the last 12 months, based on questions derived from the International Study on Asthma and Allergy in Childhood (ISAAC) (28). The Lifeways investigators collected information on ever having asthma and asthmatic symptoms in the last 12 months, instead of wheezing.

Statistical analysis

A pooled analysis of primary data from the cohorts was performed using a 2-stage approach: Cohort-specific risk ra-tios with 95% confidence intervals were calculated using Poisson regression models and then pooled to obtain an overall summary risk ratio using the DerSimonian and Laird random-effects method (29). The multivariable risk ratios were adjusted for several maternal characteristics—namely, country of birth, education, smoking during pregnancy, asthma, parity, age at child's birth, body mass index (calcu-lated as the ratio of weight (kg) to squared height (m^2)) be-fore pregnancy, hypertensive disorders of pregnancy, and diabetes (defined as either chronic diabetes before preg-nancy or overt diabetes or glucose intolerance during preg-nancy). Additionally, adjustment was made for birth year, sex, gestational age of the infant, and weight for gestational age, calculated according to Fenton fetal-infant growth charts (30) and defined as adequate, small, or large for gesta-tional age. First, we estimated the association between cesar-ean delivery (vs. vaginal delivery) and current asthma at school age by including all participating cohorts, and then we estimated the association between operative vaginal, elective, and emergency cesarean delivery (vs. spontaneous vaginal delivery) and current asthma by excluding cohorts without the specific data (INMA Menorca, KOALA). Finally, we conducted 2 sensitivity analyses restricted to: 1) children born at term (gestational age of 37–41 weeks), in order to reduce unmeasured confounding (e.g., other mater-nal complications arising during pregnancy and at birth), and 2) children born to mothers or fathers with asthma or hay fever. Participants with missing values for the outcome, exposure, or potential confounders were excluded; robust variance was estimated in the cohort-specific analysis to al-low for intragroup correlation, because women may have participated in the cohort studies with more than 1 preg-nancy. Pooled analyses were performed both by excluding the DNBC cohort and by including the DNBC cohort, be-cause of its relatively large sample size. Statistical analysis was performed using the statistical software STATA 12.1 (StataCorp LP, College Station, Texas).

RESULTS

Characteristics of the cohort participants are shown in Table 1. The total number of children with available infor-mation on current asthma at school age was 67,613. De-scriptive characteristics of the cohorts in terms of outcome and exposures are reported in Web Table 1 (available at http://aje.oxfordjournals.org/); the distribution of potential confounders of the association between mode of delivery and asthma is given in Web Table 2. Most of these variables were distributed heterogeneously between the cohorts (χ^2 test for heterogeneity: $P < 0.01$). The prevalence of current asthma varied from 3.3% in the Generation R Study and the KOALA cohort to 11.3% in the Lifeways cohort. As ex-pected, spontaneous vaginal delivery was the most common mode of delivery in all of the cohorts, varying from 47.9% in the Generation XXI cohort to 79% in the KOALA cohort. The rate of cesarean delivery varied from 9.4% in the South-ampton Women's Survey cohort to 37.5% in the Generation XXI cohort. The proportions of different modes of delivery in the cohort studies that had this information also varied greatly: The prevalence of operative vaginal delivery varied

from 5.9% in the INMA Menorca cohort to 18.7% in the Generation R cohort; the prevalence of elective cesarean de-livery varied from 4.7% in the Lifeways cohort to 17.8% in the GASPII cohort; and the prevalence of emergency cesar-ean delivery varied from 1.4% in the Southampton cohort to 20.2% in the Generation XXI cohort.

Overall crude and adjusted risk ratios for the associations between different modes of delivery and current asthma in children are shown in Table 2, while cohort-specific crude and adjusted risk ratios are reported in Web Table 3. In the pooled analysis, cesarean delivery, as opposed to vaginal delivery, was associated with a 22% increased risk of current asthma in children (95% confidence interval (CI): 2, 46) (Figure 1). As for different modes of delivery, in comparison with spontaneous vaginal delivery the risk ratio for current asthma among children born by elective cesarean delivery was 1.33 (95% CI: 1.02, 1.75) (Figure 2), and among children born by emergency cesarean delivery it was 1.07 (95% CI: 0.94, 1.22) (Figure 3). There was no evidence of an associ-ation between operative vaginal delivery and current asthma (adjusted risk ratio (aRR) = 0.97, 95% CI: 0.84, 1.12) (Figure 4). When the DNBC cohort was excluded, a higher risk ratio was observed both for cesarean delivery (aRR = 1.32, 95% CI: 1.04, 1.68) compared with vaginal delivery and for elective cesarean delivery (aRR = 1.47, 95% CI: 1.02, 2.12) compared with spontaneous vaginal delivery.

When we restricted the analysis to children born at term (50,768 out of 57,884 children included in the analyses), the risk ratio for current asthma did not change in compari-son with the main analysis for operative vaginal delivery (aRR = 0.94, 95% CI: 0.75, 1.18) or emergency cesarean delivery (aRR = 1.07, 95% CI: 0.91, 1.24), but it increased for children born by elective cesarean delivery (aRR = 1.49, 95% CI: 1.13, 1.97) (Figure 5). After the exclusion of the DNBC cohort, these results were confirmed for operative vaginal (aRR = 0.91, 95% CI: 0.62, 1.33) and emergency cesarean (aRR = 1.04, 95% CI: 0.75, 1.45) delivery and were emphasized for elective cesarean delivery (aRR = 1.63, 95% CI: 1.12, 2.38).

No difference in risk ratio estimates was observed when considering children born to mothers or fathers with asthma or hay fever, although confidence intervals were larger due to lower numbers of subjects (data not shown).

No evidence of heterogeneity in the estimated risk ratios was observed among the cohorts (all P's for heterogeneity > 0.05).

DISCUSSION

We investigated the association between mode of delivery and asthma at early school age by combining data from 9 pro-spective birth cohort studies carried out in Europe and found that cesarean delivery is associated with an increased risk of current asthma in children in comparison with vaginal deliv-ery. An increased risk of current asthma at early school age was observed among children born by elective cesarean sec-tion when compared with spontaneous vaginal delivery, and the risk was even higher in the subset of infants born at term. No increased risk of current asthma was found either for emer-gency cesarean delivery or for operative vaginal delivery.

Potential mechanisms which could explain the association between cesarean delivery and subsequent asthma and al-lergy have been recently reviewed (31). Findings from a number of recent (albeit limited in size) longitudinal studies (32–35) in different populations support previous sparse find-ings (36) that cesarean delivery is associated with disturbed gut colonization patterns up to 12–24 months of age. In one of these studies, infants born through cesarean delivery also had lower levels of T-helper 1-associated chemokines in blood (33). A body of literature in adults has established associations between dysbiosis of the gut microbiome and a wide variety of conditions and diseases, such as obesity, diabetes, and inflammatory bowel diseases (37). Although comparatively little is known about associations in children, novel investigation of the neonatal and infant gut microbiome is focused on regulation of immune defense that coevolves with the developing microbiome early in life (37).

Another mechanism that may underlie the differences in immune responses between cesarean delivery and vaginal delivery may be altered levels of stress hormones at birth. Infants delivered by cesarean section before the onset of la-bor lack the "normal" surge of stress hormones (38). These potential mechanisms may be more influential in elective ce-sarean delivery than in emergency cesarean delivery (31) because, contrary to the former, emergency cesarean deliv-ery often occurs after the onset of the labor, and hence there may be exposure to vaginal microflora and both maternal and fetal stress. Furthermore, recent data suggest that in a population of infants born at term from uncomplicated preg-nancies, elective cesarean delivery, as opposed to vaginal delivery, is associated with epigenetic alterations of neonatal CD34-positive hematopoietic stem cells, involving differen-tial DNA methylation of genes/gene regions relevant for la-ter immune-mediated diseases (39).

In a meta-analysis published in 2015, Huang et al. (40) inves-tigated the association between specific modes of delivery and the prevalence of childhood asthma. They found a 20% increase in the risk of asthma among children delivered by elective and emergency cesarean section and a 7% increase in children born by operative vaginal delivery. However, as the authors under-lined, the meta-analysis was affected by heterogeneity between studies, and some important confounders could not be taken into account. In this context, control of confounding is prob-lematic, because factors influencing the choice of mode of de-livery and potential asthma in childhood are difficult to ascertain. Two studies (8, 9) based on Swedish national health registers assessed the association between cesarean delivery and use of asthma medications or a hospital discharge diagno-sis of asthma in children by means of an age-matched sibling-pair analysis, which ideally allows control for confounding related to shared unmeasured familial factors. Using this de-sign, Almqvist et al. (8) found that the association (odds ratio (OR) = 1.24, 95% CI: 0.99, 1.60) remained for emergency cesarean delivery but not for elective cesarean delivery (OR = 0.82, 95% CI: 0.64, 0.09). In the other study, Bråbäck et al. (9) found that elective cesarean delivery still contributed to a modestly increased risk of dispensed asthma medications in preschool children (OR = 1.23, 95% CI: 1.05, 1.43), con-trary to emergency cesarean delivery, for which the associ-ation disappeared (OR = 0.95, 95% CI: 0.78, 1.14). However, drawing conclusions from these 2 studies (8, 9) requires cau-tion, because although the within-pair estimates are not af-fected by bias due to shared confounders, they could be biased by nonshared confounders (41). In our study, we ad-justed for a large set of potential confounders, including ma-ternal complications and conditions arising during pregnancy, and this only slightly reduced the observed association be-tween cesarean delivery and asthma in children. However, our estimates could still

have been affected by unmeasured con-founding, such as family environment, including maternal preference for cesarean delivery (e.g., maternal anxiety) and other medical conditions (e.g., anthropometric measures) that are indications for cesarean delivery and have been found to be associated with asthma in children (42, 43).

Nowadays women who undergo cesarean section are typ-ically pretreated with antibiotics (44), which can perturb the intestinal microflora of their infants (31). We did not have data on predelivery administration of antibiotics in our co-horts; however, it is unlikely that at the time of enrollment in most of the participating cohorts (Table 1), the policy was to administer antibiotics before skin incision rather than after umbilical cord clamping (45).

In a cohort study, Magnus et al. (7) attempted to evaluate whether the association between cesarean delivery and asth-ma in children aged 36 months could be explained by post-natal exposure, including breastfeeding; they did not find evidence of any mediation pathways. Women who undergo cesarean delivery are less likely to breast-feed (46), and ma-ternal antibodies in breast milk provide benefits to the intes-tinal immune system of the breast-fed infant which might persist into adulthood (47). Nevertheless, current evidence is inconclusive regarding the association between breastfeeding and asthma at school age (48), a condition clearly different from wheezing in preschool children. We did not adjust for breastfeeding, because adjustment for a mediator could intro-duce a spurious association between the exposure and the outcome (collider bias) in the presence of unmeasured vari-ables that confound the mediator-outcome relationship (49). However, breastfeeding could also act as a confounder, po-tentially introducing bias in our estimates; hence, we also ad-justed for breastfeeding in a sensitivity analysis, but the estimates did not change more than marginally after adjust-ment (data not shown). As expected, there was variability in the distributions of mode of delivery, confounders, and out-comes among the cohorts. In addition to a differential distri-bution in the underlying population, the observed variability might also be due to differences in study design, selection of the study population, and wording and timing of the ques-tions posed to participants. The information on mode of de-livery was extracted from obstetrical records/registers in all but 2 cohorts (which accounted for less than 3% of partici-pants), and differences in rates reflect well-known geograph-ical heterogeneities (50). Differences in asthma rates among European countries are also well known (51). The definition of current asthma at school age and the lack of data that would allow specifying the outcome as an allergic asthma phenotype versus a nonallergic phenotype could represent limitations of this study. In our analyses, asthma cases in-cluded children with both reported ever occurrence of asthma and reported wheezing or whistling in the chest during the last 12 months. Although the reported occurrence of asthma relied on physician diagnosis in most cohorts, wheezing, which is widely used in epidemiologic surveys and on which even clinicians rely primarily for diagnosis and managing asthma, might not always be well recognized by the parents (52). It is of interest, however, that in a recent register-based study, offspring born by planned cesarean delivery were at increased risk of both asthma requiring hospital admission and salbutamol inhaler prescription in comparison with chil-dren born vaginally (12)—thereby supporting our results, which were based on questionnaires.

The main strength of our study consisted of the use of in-dividual participant data from 9 European birth cohorts for assessment of the cohort-specific association between mode of delivery and asthma in children, as well as calculation of a pooled association in order to obtain greater statistical power. In the data collection phase, we also harmonized the data to reduce between-studies heterogeneity that would not reflect population differences. The homogeneity of the esti-mated associations across the different cohorts supports the robustness of the results against bias introduced by residual confounding. The prospective data collection reduced the risk of recall bias and decreased the likelihood that mothers would differentially report information on potential con-founders based on their child's disease status. Finally, unlike the case in previous studies focusing on different modes of delivery and wheezing in preschool children (7, 10), our outcome was current asthma in school-age children.

In conclusion, the large number of participants included in this study made it possible to analyze the associations of specific modes of delivery with asthma separately and to re-strict the analysis to infants born at term in order to decrease residual confounding, especially from maternal complica-tions arising in pregnancy and at birth. Cesarean delivery, particularly elective cesarean delivery, was associated with asthma at school age, and the association was stronger when the analysis was restricted to infants born at term. This infor-mation is especially relevant in light of the increased rate of elective cesarean delivery (50). No increased risk of asthma in children was found for emergency cesarean delivery or for operative vaginal delivery.

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