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

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Abbreviations: Adjusted Risk Ratio (aRR); Body Mass Index (BMI).

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ABSTRACT

Evidence on the association of modes of delivery with asthma at school age is inconclusive.

We assessed the association between specific modes of delivery and asthma in children of nine European birth cohorts who enrolled participants from 1996 to 2006.

Cohort-specific crude and adjusted Risk Ratios (aRR) for asthma at 5-9 years were calculated using Poisson regression models and pooled. A sensitivity analysis in children born at term was carried out to reduce confounding due to perinatal factors.

The study included 67,613 participants. Cohort-specific rates of cesarean varied from 9.4% to 37.5%. Cesarean section, as opposed to vaginal delivery, was associated with an increased risk of asthma (aRR, 1.22; 95% CI: 1.02,1.46). Compared to spontaneous vaginal delivery, the aRR was 1.33 (95% CI: 1.02,1.75) for elective caesarean, 1.07 (95% CI: 0.94,1.22) for emergency cesarean, and 0.97 (95% CI: 0.84,1.12) for operative vaginal delivery. In children born at term, the associations strengthened only for elective cesarean (aRR, 1.49; 95% CI: 1.13,1.97).

The large sample size allowed analysis of the association of specific modes of delivery with asthma at school age. The increased risk of asthma associated with elective caesarean, especially in children born at term, is relevant to counteract the rise in this practice, which is often performed without clear medical indication.

KEY WORDS: cesarean section; child; cohort studies.

There is increasing evidence that aspects of the prenatal and perinatal environment are involved in the aetiology of several chronic disorders, including respiratory disorders. (1) Two meta-analyses published in 2007 and 2008 found a 20% increased risk of asthma among children delivered by cesarean section. (2,3) More recently, other studies, based on prospective birth cohorts or registers linking the risk of asthma to cesarean delivery, found inconsistent results: cesarean section has been found to be associated, not associated or associated only in selected populations (such as allergic mothers) with wheezing or asthma in children. (4-12) Only few of these studies could distinguish between different modes of delivery, (4, 7-9, 11, 12) again with inconsistent results between emergency and elective caesarean. Some of these inconsistencies might arise also 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 obstetric interventions leading to vaginal delivery; a recent study on forceps delivery found an association which weakened after controlling for confounders. (13) As underlined in a recent editorial paper, the issues of long-term associations of emergency and elective caesarean with asthma or allergic diseases and whether a causal association between mode of delivery and these outcomes exists are still far from being resolved. (14) The problem lies in the fact that there are many potential factors influencing the choice of mode of delivery, including pre-pregnancy, pregnancy and perinatal medical factors, as well as preferences of the pregnant woman and clinical practice patterns. (15)

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

In the present study we assessed the association between mode of delivery and current asthma in school-aged children, pooling individual data from several prospective European birth cohorts participating in the CHICOS (Developing a Child Cohort Research Strategy for Europe) project (*http://*www.chicosproject.eu*)*, to provide

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 reduced unmeasured confounding by restricting the analysis to infants born at term.

METHODS

Potential cohorts to be included were identified through the birth cohort inventories *www.birthcohort.net* (17) and *www.birthcohortsenrieco.net* (18) and through direct contact with researchers participating in the European CHICOS project.

Birth cohorts were eligible if they had started the enrollment after 1990, and if they had suitable information on mode of delivery as well as on current asthma of children at early school age.

Cohorts that agreed to participate and who met the inclusion criteria were: Danish National Birth Cohort (DNBC) (Denmark); (19) 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) Generation R (Rotterdam, Netherlands); (22) Generation XXI (Porto, Portugal); (23) INfancia y Medio Ambiente--(Environment and Childhood) Project (INMA) (Menorca, Spain); (24) Child, parents and health: lifestyle and genetic constitution (KOALA) (Netherlands); (25) Lifeways Cross-Generation Cohort Study (Lifeways) (Dublin and Galway, Ireland); (26) Southampton Women's Survey (Southampton, United Kingdom). (27) Multiple births were excluded from the analysis, as mode of delivery and current asthma may be different in multiples.

All original cohort studies were approved by their local Ethical Committee and provided written informed consent to use their data.

Exposure and outcome assessment

Mode of delivery was classified as spontaneous vaginal, operative vaginal, elective cesarean and emergency cesarean section. INMA Menorca and KOALA cohorts collected data on mode of delivery categorized only as vaginal and cesarean without further specifications. For most cohorts, information on mode of delivery was extracted from obstetric records, while for the DNBC cohort 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 the cohorts, information on asthma and wheezing symptoms was obtained from a parental questionnaire filled in at a child age between 5 and 9 years. Current asthma was defined as ever occurrence of asthma and wheezing or whistling in the chest in the last 12 months, based on questions derived from the International Study on Asthma and Allergy in Childhood (ISAAC). (28) The Lifeways cohort collected information on asthma ever and asthmatic symptoms in the last 12 months instead of wheezing.

Statistical analysis

A pooled analysis of primary data from the cohorts was performed by a two-stage approach: cohort-specific risk ratios (RR) with 95% confidence intervals (95% CI) were calculated using Poisson regression models and then pooled in an overall summary risk ratio using the DerSimonian and Laird random effects method. (29) The multivariable RR were adjusted for several maternal characteristics, namely country of birth, education, smoking in pregnancy, asthma, parity, age at child birth, Body Mass Index (BMI, calculated as the ratio of weight (kg) to height $(m)^2$) before pregnancy, hypertensive disorders of pregnancy, and diabetes (defined as either chronic diabetes before pregnancy or overt diabetes or glucose intolerance in pregnancy). 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 (AGA), small (SGA) and large (LGA) for gestational age. First, we estimated the association between cesarean section *versus* vaginal delivery and the risk of 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 by excluding cohorts without the specific data (INMA Menorca, KOALA). Finally, we conducted two sensitivity analyses restricted to: i) children born at term (from 37 to 41 weeks of gestational age) in order to reduce unmeasured confounding (e.g. other maternal complications in pregnancy and at birth) and ii) 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 allow for intra-group correlation because women may have had participated in the cohorts with more than one pregnancy. Pooled analyses were performed both by excluding and including the DNBC cohort because of its

relatively large sample size. Statistical analysis was performed using statistical software STATA 12.1 (StataCorp LP, College Station, Texas).

RESULTS

Characteristics of the participating cohorts are reported in Table 1. The total number of children with available information on current asthma at school age was 67,613. Descriptive characteristics of the cohorts in terms of outcome and exposures are reported in Web Table 1; the distribution of the potential confounders of the association between mode of delivery and asthma are reported in Web Table 2. Most of these variables were distributed heterogeneously between the cohorts (test for heterogeneity (χ^2): P<0.01). Current asthma varied from 3.3% in the Generation R and in the KOALA cohort to 11.3% in the Lifeways cohort. As expected, spontaneous vaginal delivery was the most common mode of delivery in all the cohorts, varying from 47.9% in the Generation XXI cohort to 79% in the KOALA cohort. Cesarean section rate varied from 9.4% in the Southampton Women's Survey cohort to 37.5% in the Generation XXI cohort. The proportions of different modes of delivery in the cohorts that had this information also varied greatly: operative vaginal varied from 5.9% in the INMA Menorca cohort to 18.7% in the Generation R cohort; elective cesarean varied from 4.7% in the Lifeways cohort to 17.8% in the GASPII cohort, and emergency cesarean varied from 1.4% in the Southampton Women's Survey cohort to 20.2% in the Generation XXI cohort.

Overall crude RR and adjusted RR (aRR) for the association between different modes of delivery and current asthma in children are reported in Table 2 while cohort-specific crude RR and aRR are reported in Web Table 3. In the pooled analysis, cesarean section, as opposed to vaginal delivery, was associated with a 22% increased risk of current asthma in children (95% CI: 2%, 46%) (Fig 1). As for different modes of delivery: in comparison to spontaneous vaginal delivery the risk ratio of current asthma in children born by elective cesarean was 1.33 (95% CI: 1.02,1.75) (Fig 2), and in children born by emergency cesarean was 1.07 (95% CI: 0.94,1.22) (Fig 3). There was no evidence of an association between operative vaginal delivery and current asthma (aRR, 0.97; 95% CI: 0.84,1.12) (Fig 4). When excluding the DNBC cohort, a higher RR was observed both for cesarean section (aRR, 1.32; 95% CI: 1.04,1.68) compared to vaginal delivery and for elective cesarean (aRR, 1.47; 95% CI: 1.02, 2.12) compared to 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 RR of current asthma did not change compared with the main analysis for operative vaginal delivery (aRR, 0.94; 95% CI: 0.75, 1.18) and emergency cesarean (aRR, 1.07; 95% CI: 0.91,1.24), but it increased for children born by elective cesarean (aRR, 1.49; 95% CI:1.13,1.97) (Fig 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) and were emphasized for elective cesarean (aRR: 1.63; 95% CI: 1.12,2.38).

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

No evidence of heterogeneity among the cohorts in the estimated RRs was observed (all P values for heterogeneity >0.05).

DISCUSSION

We investigated the association between mode of delivery and asthma at early school age by combining data from nine prospective birth cohorts in Europe and found that cesarean section is associated with an increased risk of current asthma in children in comparison with vaginal delivery. An increased risk of current asthma at early school age was observed in children delivered by elective cesarean when compared with spontaneous vaginal delivery and it was even higher in the subset of infants born at term. No increased risk of current asthma was found neither for emergency cesarean nor for operative vaginal.

Potential mechanisms which could explain the association between cesarean section and subsequent asthma and allergy have been recently reviewed. (31) A number of recent, albeit limited in size, longitudinal studies (32-35) in different populations support previous sparse findings (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 section also had lower levels of the Th1-associated chemokines in blood. (33) A body of literature in adults established associations between dysbiosis of gut microbiome and a wide variety of conditions and

diseases, like obesity, diabetes and inflammatory bowel diseases (37). Although comparatively little is known in children, the 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)

The lower levels of stress hormones at birth have been also implicated in long lasting effects on asthma and allergy. (38) These potential mechanisms may be more influential in elective than in emergency cesarean (31) because, contrary to the former, emergency cesarean 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 and from uncomplicated pregnancies, elective cesarean section, as opposed to vaginal delivery, is associated with epigenetic alterations of neonatal CD34þ hematopoietic stem cells, involving differential DNA methylation of genes/gene regions relevant for later immune-mediated diseases. (39)

In a meta-analysis published in 2015, Huang et al (40) investigated the association between specific modes of delivery and the prevalence of childhood asthma. They found a 20% increase in the risk of asthma in children delivered by elective and emergency cesarean section and a 7% increase in children born by operative vaginal delivery. However, as underlined by the authors, the meta-analysis was affected by heterogeneity between studies and some important confounders could not be taken into account. In this context, the control of confounding is problematic because factors influencing the choice of mode of delivery and potential asthma in childhood are difficult to ascertain. Two studies, (8,9) based on the Swedish national health registers, assessed the association between cesarean delivery and asthma medications or discharge diagnosis in children by an age-matched sibling-pair analysis, which ideally allows control for confounding related to shared unmeasured familial factors. Using this design, in one study (8) the association (OR 1.24; 95% CI: 0.99,1.60) remained for emergency cesarean section but not for elective cesarean (OR 0.82; 95% CI: 0.64, .09), while in the other study (9) elective cesarean still contributed to a modestly increased risk of dispensed asthma medications in pre-school children (OR 1.23; 95% CI: 1.05,1.43) contrary to emergency cesarean section for which the association disappeared (OR 0.95; 95% CI: 0.78,1.14). However, such conclusions require caution because although the within-pair estimates are not affected by bias due to shared confounders, they could be biased by non-shared

confounders. (41) In our study we adjusted for a large set of potential confounders, including maternal complications and conditions in pregnancy, and this only slightly reduced the observed association between cesarean section and asthma in children. However, our estimates could still be affected by unmeasured confounding, such as family environment, including maternal preference for cesarean (e.g. maternal anxiety), and other medical conditions (e.g. anthropometric measures) which are indication for cesarean section, and have been found to be associated with asthma in children. (42,43)

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

A cohort study (7) attempted to evaluate whether the association between cesarean section and asthma in children aged 36 months could be explained by post-natal exposure, including breastfeeding; the authors did not find evidence of any mediation pathways. Women who undergo cesarean are less likely to breastfeed, (46) and maternal antibodies in breast milk provide benefits to the intestinal 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 pre-school children. We did not adjust for breastfeeding, because adjustment for a mediator could introduce a spurious association between the exposure and the outcome (collider bias) in the presence of unmeasured variables that confound the mediator-outcome relationship. (49) However, breastfeeding could also act as a confounder potentially introducing bias in our estimates; hence we also adjusted for breastfeeding in a sensitivity analysis, but estimates did not change more than marginally after adjustment (data not shown). As expected, there was variability in the distribution of mode of delivery, confounders and outcomes among the cohorts. In addition to a differential distribution in the underline population, the observed variability might also be due to differences in the study design, selection of the study population, as well as to wording and timing of the questions. The information on mode of delivery was extracted from obstetric records/registers in all but two cohorts which accounted for less than 3% of participants, and differences in rates reflect well known

geographical 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 versus non-allergic asthma phenotype could represent limitations of this study. In our analyses, asthma cases included children with both reported ever occurrence of asthma and reported wheezing or whistling in the chest in the last 12 months. Although the reported occurrence of asthma relied on doctor 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 were at increased risk of both asthma requiring hospital admission and salbutamol inhaler prescription in comparison with children born vaginally, thereby supporting our results that are based on questionnaires. (12)

The main strength of our study consists of using individual participant data from nine European birth cohorts in order to assess the cohort-specific association between mode of delivery and asthma in children as well as a pooled association in order to obtain a higher statistical power. In the data collection phase, data were also harmonized to reduce between-studies heterogeneity that would not reflect population differences. The homogeneity of the estimated 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 confounders based on their child's disease status. Finally, unlike previous studies focusing on different modes of delivery and wheezing in pre-school children, (7,10) our outcome was current asthma in school-aged children.

Conclusions

The large number of participants included in this study made it possible to analyze the associations of the specific modes of delivery with asthma separately, and to restrict the analysis to infants born at term in order to decrease residual confounding, especially from maternal complications in pregnancy and at birth. Cesarean section, and in particular elective cesarean section, was associated with asthma at school age, and the association was stronger when the analysis was restricted to infants born at term. This information is relevant

especially in light of the increased rate of elective cesarean. (50) No increased risk of asthma in children was found for emergency cesarean and for operative vaginal delivery.

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Table 1**.** Descriptive Characteristics of the Nine European Birth Cohorts Participating in the Study (years of enrolment 1996-2006).

Cohort	Reference	Country	Enrolment		No of Participants[a]
			Years	Developmental period	
DNBC	19	Denmark	1996-2002	Pregnancy	52,351
EDEN	20	France	2003-2006	Pregnancy	1,122
GASPII	21	Italy	2003-2004	Birth	455
Generation R	22	Netherlands	2001-2006	Pregnancy/birth	4,338
Generation XXI	23	Portugal	2005-2006	Pregnancy/birth	5,696
INMA Menorca	24	Spain	1997-1998	Pregnancy	444
KOALA	25	Netherlands	2000-2003	Pregnancy	1,842
Lifeways	26	Ireland	2001-2003	Pregnancy	426
Southampton Women's Survey	27	UK	1998-2002	Pre-pregnancy	939

Abbreviations: 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; Lifeways, Lifeways Cross-Generation Cohort Study.

[a] Number of children with information on current asthma at school age.

Table 2. Crude and Adjusted Risk Ratios for Current Asthma at School Age by Mode of Delivery in Nine European Birth Cohorts Participating in the Study (years of enrolment 1996-2006).

Mode of delivery	**Crude RR**	**95% CI**	**Adjusted[a] RR**	**95% CI**
Vaginal	1.00	ref	1.00	ref
Caesarean	1.30	1.10-1.55	1.22	1.02, 1.46
Spontaneous vaginal	1.00	ref	1.00	ref
Operative vaginal	0.89	0.70-1.13	0.97	0.84, 1.12
Elective Caesarean	1.37	1.10-1.72	1.33	1.02, 1.75
Emergency Caesarean	1.12	0.86-1.44	1.07	0.94, 1.22

Abbreviations: RR, risk ratio; 95% CI, 95% confidence interval.

[a]: Adjusted for country of birth, maternal education, smoking in pregnancy, asthma parity, age at child birth, BMI, hypertensive disorders of pregnancy, diabetes, birth year, gestational age of the infant, infant sex, and weight for gestational age.

FIGURES LEGEND

Figure 1. Association between cesarean section and current asthma in children in nine European birth cohorts. RR: Cohort specific and pooled mutually adjusted risk ratios; 95% CI, 95% confidence interval; Estimated Predictive Interval: region in which about 95% of the true study effects are expected to be found. Percentage of between-studies heterogeneity: I^2 = 27.0%, P = 0.204.

SWS: Southampton Women's Survey

Figure 2. Association between elective cesarean and current asthma in children. I^2= 44.0%, *P* = 0.098.

Figure 3. Association between emergency cesarean and current asthma in children. I^2= 0.0%, *P* = 0.898.

Figure 4. Association between operative vaginal and current asthma in children. I^2= 0.0%, *P* = 0.488.

Figure 5. Association between elective cesarean and current asthma in children born at term. I^2= 15.4%, *P* = 0.312.