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Association between preterm birth and intrauterine growth retardation and child asthma

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ABSTRACT: An association between preterm birth and an increased risk of childhood asthma has been demonstrated, but the importance of intrauterine growth retardation on asthma risk is unclear.

Using data from Swedish health registers, infant characteristics and childhood asthma were studied. Analyses were made using Mantel–Haenszel methodology with adjustment for year of birth, maternal age, parity, smoking in early pregnancy and maternal body mass index. Preterm birth, birth weight and birth weight for gestational week were analysed and childhood asthma was evaluated from prescriptions of anti-asthmatic drugs. Neonatal respiratory problems and treatment for them were studied as mediating factors.

Both short gestational duration and intrauterine growth retardation appeared to be risk factors and seemed to act separately. The largest effect was seen from short gestational duration. Use of mechanical ventilation in the newborn period and bronchopulmonary dysplasia were strong risk factors. A moderately increased risk was also seen in infants born large for gestational age.

We conclude that preterm birth is a stronger risk factor for childhood asthma than intrauterine growth disturbances; however, the latter also affects the risk, and is also seen in infants born at term.

KEYWORDS: Birth weight, epidemiology, mechanical ventilation, registers, respiratory problems

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Many publications have investigated the asthma risk in individuals born preterm or with low birth weight (review in [1]). Most studies have investigated short gestational duration or low birth weight, but some refer also to the effect of intrauterine growth retardation (IUGR) [2–5].

Two large recent studies, both from Sweden, have investigated this question and reached different results in spite of similar materials studied [6, 7]. In the first paper, only extreme preterm birth (<28 weeks) was associated with an increased risk of asthma; in the latter study, a continuous decline in asthma risk was seen with increasing gestational duration, statistically significant even at 37–38 weeks compared to the reference 39–41 weeks.

In the present study, we have separated the effect of short gestational duration and low birth weight from IUGR on asthma risk.

MATERIAL AND METHODS

We used information in the Swedish Medical Birth Register [8] in order to identify children surviving the neonatal period, who were born preterm and/or had a disturbed intrauterine growth. Pregnancy duration as recorded in the register was, in most instances, based on second-trimester ultrasound or, if absent, on the last menstrual period. Intrauterine growth deviation was expressed as a standard deviation score (SDS) from the normal birth weight at a specific week, estimated according to data in the register [9]. Comparisons were also made with the normal graph published by MARSÁL *et al*. [10], which gave similar results (not shown). IUGR was defined as <2 standard deviations below the normal weight at that gestational week.

This register also gave information on variables that were used in the adjusted analyses: year of delivery, maternal age, parity, smoking habits in early pregnancy, maternal pre-pregnancy body mass index (BMI), maternal country of birth and sex of infant. Information on smoking in early pregnancy and pre-pregnancy BMI was obtained by midwife interviews at the first antenatal visit, usually before the end of the first trimester.

In order to identify asthma in the children, the Swedish Prescribed Drug Register [11] was used. This register covers all prescriptions filled in Sweden since July 1, 2005 and individuals who

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had received prescriptions for anti-asthmatic drugs (Anatomical Therapeutic Chemical code R03) were identified from that date until the end of 2008. In order to increase the probability that the drugs had been prescribed for asthma and not for unrelated complaints, prescriptions made on five or more different occasions were used as a definition of asthma. The age of the children varied between 2 and 11 yrs when asthma was identified.

The association between gestational duration and asthma risk was studied in singletons with known gestational duration and infant sex whose mothers were born in Sweden. The Mantel–Haenszel technique was used to adjust for year of birth, maternal age, parity, smoking in early pregnancy, maternal pre-pregnancy BMI and infant sex. The adjustment for infant sex was made because the sex ratio declines with gestational week of delivery and there is a male excess in children who are prescribed drugs for asthma. As a reference group, pregnancy duration between 39 and 41 weeks was used. Separate estimates were made for males and females, and analyses were repeated with restriction to infants with a SDS between -1 and 1 SD from the expected weight given pregnancy week of birth, infant sex and parity.

The association between infant birth weight and asthma risk was adjusted in the same way and we used 3,000–3,999 g as a reference. The analyses were repeated separately for males and females and with restriction to infants with a SDS between -1 and 1 SD from the expected weight given pregnancy week, infant sex and parity.

The association between infant intrauterine growth and asthma risk was adjusted in the same way and we used the SDS -1–1 as a reference. The analyses were made separately for males and females and were repeated with restriction to infants born at 39–41 weeks duration.

The impact of neonatal respiratory diagnoses, mechanical ventilation, continuous positive airway pressure (CPAP) treatment and chorioamnionitis was investigated after adjustment for year of birth, maternal age, parity, smoking in early pregnancy, maternal BMI, infant sex and gestational duration (classified as in table 1). Respiratory diagnoses were defined as specific codes according to the International Classification of Diseases (ICD)-10, P21–P28. P21 defines birth asphyxia, P22 respiratory distress of the newborn, P23 congenital pneumonia, P24 neonatal aspiration syndrome, P25 interstitial emphysema and related conditions, P26 pulmonary haemorrhage, P27 chronic respiratory disease, and P28 other respiratory conditions, all originating in the perinatal period. The presence of chorioamnionitis was identified from the ICD-10 code O41.1.

Ethics

The study was performed within the responsibilities of the National Board of Health and Welfare (Stockholm, Sweden) and therefore no ethical approval from outside ethical committees was needed.

RESULTS

The study on gestational duration was made on 765,792 children. Among them, 43,387 (5.7%) were identified as having filled at least five prescriptions for anti-asthmatic drugs during the study period. The material used for the study of intrauterine growth was slightly smaller (because of some unknown birth weights): the total number of children was 763,666, among whom 43,184 (5.7%) had filled at least five prescriptions.

There is a male excess at preterm birth (sex ratio 1.19, 95% CI 1.17–1.22; the sex ratio among all infants born in weeks 39–41 is 1.03). There is also a male excess among children who had five or more prescriptions for anti-asthmatic drugs (sex ratio 1.67, 95% CI 1.57–1.79).

Table 1 shows data for the association between gestational duration and the use of anti-asthmatics. The asthma risk decreases with increasing gestational duration at birth and is slightly decreased among post-term births. Similar findings based on birth-weight data are seen in table 2. Risk estimates are however lower than those for gestational duration.

Intrauterine growth changes, estimated as SDSs of birth weight at each gestational duration, also affected the risk for asthma (table 3). The effects on asthma risk were lower than those for gestational duration.

As short gestational duration, birth weight and IUGR are associated, the analysis of the effect of gestational duration or birth weight on asthma risk was repeated with a restriction to children who had not deviated markedly in intrauterine growth at birth (SDS -1–1) (tables 1 and 2). The estimated odds ratios were relatively similar to those obtained without restrictions based on intrauterine growth, but confidence intervals were wider.

Similarly, the effect of disturbed intrauterine growth (estimated as SDS of birth weight from expected weight at that gestational week) was analysed, restricted to children who were born in weeks 39–41 (table 3). When these data were compared with those obtained without restrictions to pregnancy duration, no marked differences appeared.

In order to study possible confounding from maternal asthma, females who had reported the use of anti-asthmatic drugs in early pregnancy were removed from the analysis (n=13,897). Only small changes in the estimated odds ratios were seen (data not shown).

The various analyses were run separately for males and females but no consistent difference between sexes in asthma risk associated with gestational duration or intrauterine growth was noted (data not shown).

Table 4 presents the results of the effect of respiratory diagnosis, mechanical ventilation and CPAP on asthma risk. The highest risk estimate was found after bronchopulmonary dysplasia. The risk was also high after mechanical ventilation. Also, in the absence of a recorded mechanical ventilation or CPAP procedure, an increased asthma risk was found.

The effect of chorioamnionitis did not reach statistical significance. There were 98 infants with such a maternal diagnosis and childhood asthma, and 982 among all infants born. The adjusted odds ratio was 1.25 (95% CI 0.97–1.61).

TABLE 1 Number of children in population and number with asthma according to gestational week at birth

Gestational age weeks	All children			Children with SDS -1–1		
	Population	With asthma	OR (95% CI)	Population	With asthma	OR (95% CI)
23–27	1570	280	4.06 (3.59–4.59)	650	121	4.17 (3.45–5.05)
28–30	2454	329	2.87 (2.56–3.22)	1045	156	3.25 (2.75–3.83)
31–32	3157	363	2.28 (2.05–2.54)	1602	174	2.22 (1.90–2.59)
33–34	7656	804	2.11 (1.96–2.27)	4305	474	2.28 (2.07–2.50)
35–36	23594	1985	1.70 (1.62–1.78)	14405	1191	1.70 (1.59–1.80)
37–38	141683	9323	1.43 (1.39–1.47)	90190	5724	1.38 (1.34–1.43)
39–41	528793	27439	1.00 (reference)	342941	17771	1.00 (reference)
42–44	56885	2864	0.89 (0.86–0.93)	35545	1757	0.90 (0.85–0.94)
Total	765792	43387		490683	27368	

Data are presented as n, unless otherwise stated. Data were adjusted for year of birth, maternal age, parity, smoking in early pregnancy, pre-pregnancy body mass index and sex of infant. SDS: standard deviation score.

DISCUSSION

Our results indicated that both preterm birth and IUGR are risk factors for childhood asthma. The strongest effects were seen in preterm birth and also in infants who showed no marked deviation in intrauterine growth. A weaker effect was seen in small-for-date infants, also when born at term. Also infants who were large for gestational age seemed to show a moderately increased asthma risk.

The present study is large and it has been possible to adjust for a number of putative confounders. The identification of asthma in the children relied on prescription of anti-asthmatic drugs. These may be used for other medical problems than asthma, which would dilute the material with non-asthma cases. By restricting the definition to the filling of at least five prescriptions during the observation period, the proportion of true asthma cases should reasonably increase but some non-asthma cases may still have been included in the asthma group. This will result in a bias of the odds ratio estimates towards 1.0, if there is no effect on the non-asthma cases. Many studies have used prescription of anti-asthmatic drugs for the definition of asthma in register studies [6, 7, 12, 13]. One study compared the physician diagnosis of asthma with the prescription of anti-asthmatic drugs and found slightly more potential asthmatics based on prescription data than on physician diagnosis, but the sensitivity was 91% and the specificity 98% [14].

Most studies on premature birth and asthma in the offspring have indicated an association even though the risk estimates have varied [1]. Less attention has been paid to the possible effect of intrauterine growth disturbances for the origin of child asthma. Three studies [2, 4, 15] found no clear effect of IUGR, but in a twin study it was demonstrated that IUGR increased the asthma risk [5], and in a study of prematurely born infants, the presence of IUGR increased the risk for asthma [3]. In a recent study [6], adjustment for intrauterine fetal growth removed the effect of short gestational age on asthma risk, except for the shortest stratum, 23–27 weeks gestation.

TABLE 2 Number of children in population and number with asthma according to birth weight

Birth weight g	All children			Children with SDS -1–1		
	Population	With asthma	OR (95% CI)	Population	With asthma	OR (95% CI)
<1000	1758	269	3.23 (2.85–3.66)	502	86	3.78 (3.02–4.73)
1000–1499	2540	333	2.68 (2.39–3.00)	910	142	3.55 (2.48–4.23)
1500–2499	19046	1783	1.91 (1.81–2.01)	6254	670	2.20 (2.03–2.38)
2500–2999	70462	4466	1.30 (1.28–1.34)	26439	1881	1.49 (1.41–1.53)
3000–3999	509075	27379	1.00 (reference)	427043	22585	1.00 (reference)
4000–4999	156838	8765	0.94 (0.92–0.97)	35564	1961	0.94 (0.92–0.97)
5000–6499	4485	251	0.88 (0.77–1.00)			
⩾6500	5	0				
Total	764209	43264		496712	27325	

Data are presented as n, unless otherwise stated. Data were adjusted for year of birth, maternal age, parity, smoking in early pregnancy, pre-pregnancy body mass index and sex of infant. SDS: standard deviation score.

TABLE 3 Number of children in population and number with asthma according to intrauterine growth, expressed as standard deviations from expected birth weight at that week

SDS	All children			Children with gestational duration 39–41 weeks		
	Population	With asthma	OR (95% CI)	Population	With asthma	OR (95% CI)
>-5–⩽-3	1791	156	1.49 (1.26–1.76)	406	39	1.87 (1.36–2.57)
>-3–⩽-2	11581	892	1.44 (1.34–1.54)	6086	380	1.24 (1.11–1.37)
>-2–⩽-1	77080	4564	1.10 (1.06–1.14)	51751	2724	1.04 (1.00–1.09)
>-1–1	497491	27389	1.00 (reference)	349240	17764	1.00 (reference)
>1–⩽2	130636	7386	1.02 (0.99–1.05)	90999	4738	1.01 (0.98–1.05)
>2–⩽3	36072	2226	1.10 (1.05–1.15)	24030	1340	1.08 (1.02–1.14)
>3	9015	571	1.11 (1.01–1.21)	4906	301	1.15 (1.02–1.29)
Total	763666	43184		527498	27286	

Data are presented as n, unless otherwise stated. Data were adjusted for year of birth, maternal age, parity, smoking in early pregnancy, pre-pregnancy body mass index and sex of infant. SDS: standard deviation score.

There is a strong interaction between short gestational duration and IUGR: fetuses with impaired intrauterine growth have a tendency to be born preterm, either iatrogenically or because of placental insufficiency. It is therefore difficult to study the two phenomena independently. In the present study, both short gestational duration and IUGR were associated with an increased asthma risk. In order to separate the two variables, the effect of gestational duration was studied in children who had shown no signs of major intrauterine growth deviation (from -1 to 1 standard deviation from expected weight) and the effect of intrauterine growth deviation in term children, born at 39–41 weeks gestation. Children who had shown no major deviation in intrauterine growth but were born after short gestational duration or with low birth weight had a higher asthma risk than children who were born term with signs of IUGR. Both factors thus seem to be of importance even though short gestational duration appears to be the dominating one.

TABLE 4 Risk for asthma in children with respiratory problems in the neonatal period

Group of children	With asthma	Total number	OR (95% CI)
Respiratory diagnosis			
Mechanical ventilation or CPAP	2762	29827	1.33 (1.26–1.39)
No mechanical ventilation or CPAP	2276	25921	1.32 (1.26–1.39)
CPAP	419	3508	1.22 (1.07–1.39)
Mechanical ventilation	126	710	1.85 (1.44–2.31)
Bronchopulmonary dysplasia	39	176	1.97 (1.12–3.47)

Data are presented as n, unless otherwise stated. Data are shown after adjustment for year of birth, maternal age, parity, smoking in early pregnancy, maternal body mass index and gestational duration (groups as in tables 1 and 3). Children with asthma (five or more prescriptions) n=43,387, total children n=765,792. CPAP: continuous positive airway pressure.

Post-term birth or high birth weight was associated with a decrease in asthma risk but children born large for gestational age showed a moderately increased risk. In a previous study, large birth weight was associated with a decreased asthma risk [16] but post-term or large-for-date infants were not studied. That paper also found a possibly increased risk at extremely high birth weights (>6.5 kg) but statistical significance was not reached. Only a few such infants were included in the present study.

Various explanations of the association between preterm birth and an increased risk for asthma have been discussed [1] and there are probably complex causal pathways. The risk increase is probably not due to atopy, which is reduced in incidence after preterm birth [17]. One possible model [1] is a direct effect of preterm birth *per se* on asthma risk, regardless of obstetric risk factors such as chorioamnionitis [18] or post-natal complications as respiratory diseases and post-natal asphyxia, as discussed below. Premature birth *per se* leads to both transient and persistent changes in lung development [19], which can make the lungs more susceptible to later asthma-causing exposures. The post-natal growth rate was also of importance in an animal model [20].

Another model [1] implies that genetics or conditions during pregnancy resulted in both preterm birth and an increased risk for asthma. Parental asthma increases the child's risk of asthma due to genetics and, as maternal asthma is associated with an increased risk for preterm birth [21], maternal asthma could act as a confounder. Exclusion of females who had reported the use of anti-asthmatic drugs in early pregnancy hardly affected the risk estimate for child asthma, however. Some maternal factors like smoking are associated with a moderately increased risk for preterm birth and may be causal in the origin of child asthma [15]. We therefore adjusted for maternal smoking and we did the same for maternal age, parity and BMI.

The main reason for our study was not to identify the relevant mechanisms but to try to separate the effect of preterm birth

and IUGR. Neonatal respiratory problems are common in infants born preterm and we found that the presence of a neonatal respiratory diagnosis increased the asthma risk after adjustment for gestational duration, notably when mechanical ventilation had been needed and/or bronchopulmonary dysplasia was present. Mechanical ventilation has previously been shown to be a risk factor for asthma among infants with a birth weight <1,500 g [22]. Whether the effect we found was due to the procedure or the occurrence of more severe respiratory problems could not be concluded. It is, however, noticeable that the use of CPAP did not further increase the asthma risk.

As the development of the alveoli and the small airways occurs late in fetal life and post-natally, preterm birth and neonatal factors associated with it may result in lung damage that, later in life, increases the risk for asthma [23, 24]. Experimentally, even a short period of mechanical ventilation resulted in a persistent bronchiolar remodelling, which may increase the risk for future asthma development [25]. The significance of bronchopulmonary dysplasia for future asthma risk has also been stressed [26].

An increased asthma risk has been described in children who were exposed to chorioamnionitis [18]. We found a moderately increased risk but statistical significance was not reached.

IUGR also seems to be a risk factor for asthma among term infants. Various possible explanations for such an association have been discussed. Normal lung development depends on the presence of appropriate oxygen tension and nutrition and, thus, lung anomalies may occur in individuals with IUGR that increase the risk of asthma [27]. Using magnetic resonance imaging, reduced lung volume was found in fetuses that had intrauterine growth restrictions [28]. In experiments with rats, an increase in inflammatory and profibrotic processes was found after protein restriction during gestation, leading to IUGR, and thus affected future lung function [29].

In conclusion, our analysis suggests that even though IUGR is associated with an increased risk of asthma, short gestational duration even in the absence of marked IUGR is a stronger risk factor. The immaturity of the lungs in infants born preterm and/or the necessary treatment may cause permanent damage which increases the risk for childhood asthma.

STATEMENT OF INTEREST

None declared.

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