

The Burden of Childhood Asthma and Late Preterm and Early Term Births

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Objective To evaluate the association between gestational age at birth and the risk of subsequent development of asthma.

Study design We conducted a retrospective observational hospital-based birth case-control study in a university-based obstetrics and gynecology department in Finland. A total of 44 173 women delivering between 1989 and 2008 were linked with the social insurance register to identify asthma reimbursements for their offspring (n = 2661). Pregnancy factors were recorded during pregnancy. Infants were categorized as moderately preterm (≤ 32 weeks), late preterm (33–36 weeks), early term (37–38 weeks), term (39–40 weeks), or late term and postterm (≥ 41 weeks). The main outcome measure was asthma among the infants.

Results Children born moderately preterm (≤ 32 weeks gestation) had a significantly increased risk of asthma (aOR, 3.9; 95% CI, 3.2–4.8). The risk of asthma was also increased in those born late preterm (aOR, 1.7; 95% CI, 1.4–2.0) and early term (aOR, 1.2; 95% CI, 1.1–1.4). In contrast, delivery at 41 weeks or later seemed to decrease the risk of asthma (aOR, 0.9; 95% CI, 0.8–1.0). The burden of asthma associated with preterm birth was associated mainly with early term infants, in whom 108 extra cases of asthma were observed.

Conclusion Even though the individual risk of asthma was inversely correlated with gestational age at birth, the overall burden brought about by delivery before term was associated with late preterm and early term deliveries. Furthermore, delivery after term was protective against asthma. (*J Pediatr* 2013; ■: ■–■).

Asthma in children is a common disease with significant health and societal costs. Both genetic and environmental factors have roles in its development.^{1,2} Prenatal programming, immunologic changes, and immune development already determined in utero may further influence the risk.^{3,4}

Several factors during pregnancy may be of importance. Maternal stress and anxiety (indicators of prenatal stress) may program the development of asthma⁵ and, through the regulation of fetal endocrinology, decrease serum cortisol levels in the fetus, leading to the development of an allergic phenotype.¹ Maternal infections, such as chorioamnionitis, during pregnancy can lead to an altered cytokine milieu that may play a role in the development of asthma in offspring.⁶ Maternal hypertension and diabetes are known to be related to an altered inflammatory state and are associated with wheezing in childhood.⁷ Furthermore, gestational age, method of delivery, birth order, and weight have been associated with the risk of childhood asthma.^{1,6,8} Neonatal respiratory morbidity at term also is associated with an increased risk of asthma in childhood.⁹

Gestational age at birth is the most significant determinant of asthma. A recent large British cohort study found a decline in health outcomes with decreasing gestational age at birth, with asthma and wheezing showing a gradient of effect with increasing prematurity.¹⁰ These risks appeared to be strongest in early childhood and decreased later in life.¹¹

The purpose of the present study was to evaluate the role of gestational age at birth in the development of childhood asthma. We conducted an observational hospital-based birth case-control study to examine the association between gestational age at birth and the risks of asthma in childhood.

Methods

The study population was derived from a clinical birth database comprising a total population of 45 030 infants born after 22 completed weeks of gestation at Kuopio University Hospital between 1989 and 2008 (Table I). Stillbirths (n = 193), neonatal deaths (n = 177), and cases with missing data (n = 487) were excluded. Data on 44 173 women with live-born infants were linked with data from the register for reimbursement at the Social Insurance Institution of Finland for asthma medication for their offspring aged 0–19 years. Controls were women with live-born infants without asthma. The infants were categorized as very preterm (< 28 completed weeks of gestation), moderately preterm (28–32 weeks of gestation), late preterm (33–36 weeks of gestation), early term (37–38 weeks of gestation), term (39–40 weeks of gestation), late term (41 weeks of gestation), or postterm (≥ 42 weeks of gestation).

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Table I. Basic characteristics of the study population in relation to asthma at any time

	Control (n = 41 512)	Asthma (n = 2661; 6%)	P value
Primipara, n (%)	17 075 (41.1)	1043 (39.2)	.049
Maternal disease, n (%)			
Asthma	1248 (3.0)	117 (4.4)	<.001
Chronic disease*	3878 (9.3)	278 (10.4)	.058
Diabetes mellitus	242 (0.6)	21 (0.8)	.180
Gestational diabetes mellitus	3287 (7.9)	145 (5.4)	<.001
Hypertension	809 (1.9)	78 (2.9)	.001
Epilepsy†	327 (0.9)	22 (0.9)	.994
ART‡	1864 (4.5)	183 (6.9)	<.001
Maternal age, y, mean (± 2 SD)	29.0 (5.5)	28.7 (5.3)	.004
Maternal smoking (>5 cigarettes/day), n (%)			
Before pregnancy	9202 (22.2)	576 (21.6)	.530
During pregnancy	2265 (5.5)	189 (7.1)	<.001
Prepregnancy body mass index, mean (± 2 SD)§	23.3 (4.7)	23.4 (4.5)	.236
Number of previous pregnancies, mean (± 2 SD)	1.44 (1.63)	1.50 (1.60)	.129
Number of previous deliveries, mean (± 2 SD)	1.04 (1.31)	1.06 (1.24)	.498
Marital status, n (%)			
Unmarried	15 750 (37.9)	908 (34.1)	
Married	25 762 (62.1)	1753 (65.9)	<.001
Mode of delivery, n (%)			
Vaginal	33 981 (81.9)	2053 (77.2)	
Cesarean	7531 (18.1)	608 (22.8)	<.001
Singleton, n (%)	39 992 (96.3)	2518 (94.6)	
Twin, n (%)	1441 (3.5)	135 (5.1)	
Triplet, n (%)	79 (0.2)	8 (0.3)	<.001
Boy, n (%)	20 939 (50.4)	1612 (60.6)	
Gestational age, wk, mean (± 2 SD)	39.2 (2.2)	38.4 (3.3)	<.001
Birth weight, g, mean (± 2 SD)	3481 (616)	3341 (812)	<.001
Birth height, cm, mean (± 2 SD)	49.9 (4.5)	49.3 (3.7)	<.001
Head circumference, cm, mean (± 2 SD)	34.9 (1.8)	34.6 (2.4)	<.001
Abdominal circumference, cm, mean (± 2 SD)	33.8 (2.1)	33.7 (2.1)	.001
Apgar score 1 min <7, n (%)	2063 (5.0)	225 (8.6)	<.001
Apgar score 5 min <7, n (%)	806 (1.9)	73 (2.7)	.004
Age at disease onset, y, mean (± 2 SD)		4.2 (3.6)	
Asthma prevalence by age group, n (%)			
0-6 y	16 237 (39.1)	482 (18.1)	
7-12 y	10 822 (26.1)	997 (37.5)	
≥13 y	14 455 (34.8)	1182 (44.4)	

P values obtained in the univariate model.

*Including chronic bowel disease, hypothyroidism, and autoimmune diseases.

†Data available for 1989-2007.

‡ART includes in vitro fertilization, intracytoplasmic sperm injection, insemination, and ovulation induction by clomiphene and other medicines.

§Data missing in 1984 cases (4.5%).

Information on maternal prepregnancy characteristics was based on data from a self-administered questionnaire at 20 weeks of pregnancy. Public health nurses and midwives completed missing data by way of interview during visits to prenatal maternal clinics or labor wards at Kuopio University Hospital. The questionnaire consisted of 75 background items. Nurses and midwives present during delivery and the neonatal period added information on pregnancy complications, pregnancy outcome, and the neonatal period to the database. All childbearing women gave informed consent for the register study at the time of

data collection. The participation rate for delivery and neonatal items was 100%.

Information on the need for antiasthma drugs during childhood was obtained from the Drug Prescription Register maintained by the Social Insurance Institution. In Finland, to be eligible to receive reimbursement payments under the Special Refund Categories, a patient must obtain a certificate from a doctor, and the disorder must be based on clinical diagnosis and standardized criteria (*International Statistical Classification of Diseases and Related Health Problems, 10th Revision*). For children, an asthma certificate is usually provided by a pediatrician to confirm the nature of the disease and the need for medication. Antiasthma drugs are 72% reimbursed.¹²

Statistical analyses were performed using SPSS 17.0 for Windows (SPSS, Chicago, Illinois). The χ^2 and Mann-Whitney *U* tests were used to assess differences between the study and control groups. Logistic regression analysis was used to investigate multivariate-adjusted associations between gestational age at birth and diagnosis of asthma. The analyses were adjusted for maternal asthma, diabetes mellitus, gestational diabetes mellitus, hypertension, chronic diseases (eg, chronic bowel disease, hypothyroidism) at the time of pregnancy (no vs yes), maternal age (≤ 25 , 26-35, ≥ 36 years), maternal parity (0, 1 vs ≥ 2), prepregnancy body mass index (< 21 , 22-24, ≥ 25 kg/m²), smoking during pregnancy (no vs yes, smoking > 5 cigarettes per day), marital status (unmarried vs married), and assisted reproduction technology (ART; no vs yes). Further confounding factors included the child's sex, child's age (0-6, 7-12, ≥ 13 years), umbilical cord length (≤ 55 vs > 55 cm), Apgar score at 5 minutes (< 7 vs 7-10), mode of delivery (vaginal vs cesarean), and number of fetuses (single, twin, or triplet pregnancies). Gestational age at the time of delivery was further categorized as ≤ 32 , 33-36, 37-38, 39-40, or ≥ 41 weeks. The reference gestational age at birth for each disease was 40 weeks (Table II; available at www.jpeds.com) or 39-40 weeks (Table III). In Table IV, the reference gestational age was selected from Table III, where the incidence of asthma was lowest after 41 weeks of gestation. A *P* value of .05 was deemed statistically significant.

To examine whether background information (ie, mode of delivery, maternal smoking, ART, fetal sex, and maternal asthma, epilepsy, or diabetes mellitus) contributed to the differences in childhood asthma incidence related to gestational age at birth, we estimated the contribution of each of these factors by using logistic regression and comparing the percentage reductions in OR. Each confounder was added separately to model 2, and the contribution of each factor (models A/B/C/D/E) was measured by the percentage reduction in OR of childhood asthma.¹³ The following formula was used: (OR model 2 – OR model X [A/B/C/D/E])/(OR model 2 – 1) (Table IV). We estimated the extra cases of asthma among offspring because of prematurity using the following formula: (n [asthma/1000 deliveries] – n [reference asthma group] × n [total number of deliveries])/1000 (Table V).

Table III. Association between gestational age at birth and risk of asthma at any time

	Gestational age, wk	Total (n = 44 173) n (%)	Asthma (n = 2661) n (%)	aOR* (95% CI)	P value
Very and moderately preterm	≤32	968 (2.2)	172 (17.8)	3.9 (3.2-4.8)	.001
Late preterm	33-36	2355 (5.3)	213 (9.0)	1.7 (1.4-2.0)	.001
Early term	37-38	7704 (17.4)	506 (6.6)	1.2 (1.1-1.4)	.001
Term	39-40	22 804 (51.6)	1255 (5.5)	1	
Late term and postterm	≥41	10 342 (23.4)	515 (5.0)	0.9 (0.8-1.0)	.010

P values in adjusted analysis obtained from the trend test (Wald) in logistic regression models.

*Adjusted for maternal factors (asthma, diabetes mellitus, gestational diabetes mellitus, hypertension, chronic disease, age, parity, prepregnancy body mass index, smoking, marital status, and ART) and neonatal factors (sex, gestational age at birth, umbilical cord length, Apgar score at 5 minutes, mode of delivery, and number of fetuses).

The study was approved by the hospital's Institutional Review Board and the Pohjois-Savo Committee of Research Ethics (reference 93/2008).

Results

Of the 44 173 live-born children, 2661 (6.0%) had asthma during childhood (**Table I**). The mean age of onset of asthma was 4.2 years, and more than 80% of the children with asthma were aged >7 years. **Table I** shows that compared with controls, children with asthma were more frequently males and were born more frequently by cesarean delivery, at a lower gestational age, with lower Apgar scores, and to married couples vs controls. Mothers of children with asthma smoked more during pregnancy and had received more infertility treatments before pregnancy compared with the control group. Asthma was more prevalent in children whose mothers had asthma, hypertension, or pregnancy without gestational diabetes mellitus.

We evaluated the significance of different gestational ages at birth by multivariate analysis (**Tables II** and **III**). The risk of asthma was highest in children born before 32 weeks gestation compared with children born at term (aOR, 3.9; 95% CI, 3.2-4.8). The risk was also significantly higher in those born late preterm and those born early term (aOR, 1.7; 95% CI, 1.4-2.0 and aOR, 1.2; 95% CI, 1.1-1.4, respectively). In contrast, delivery at ≥41 weeks gestation apparently protect offspring from asthma (aOR, 0.9; 95% CI, 0.8-1.0). **Table IV** shows that maternal asthma and male sex had stronger effects on the risk of asthma in offspring born after 37 weeks gestation. It also identifies gestational age at birth as an independent risk factor for asthma in offspring, with other factors, such as maternal smoking, fetal sex, ART, and mode of delivery, explaining 10%-20% of the excess risk associated with preterm delivery in different pregnancy groups.

Table V presents the analysis of overall asthma burden by gestational age. It shows that late preterm (n = 91, 25% of all extra cases) and early term deliveries (n = 108, 29.7% of all extra cases) contributed most to the extra cases of asthma compared with the reference group of term infants (≥40 weeks).

Discussion

The overall prevalence of childhood asthma in our study cohort was 6%, which corresponds closely to the expected rate in Finland.¹⁴ We report 3 main findings. First, the risk of asthma was 3.9-fold higher in children born at <32 weeks gestation compared with controls, and it remained high in those born at up to 38 weeks gestation. Second, delivery after 41 weeks seemed to protect offspring from asthma. Third, the burden of asthma in offspring was associated mainly with deliveries at 37-38 weeks gestation, even though the relative risk of asthma was higher in infants born before 32 weeks. Interestingly, 151 of the 364 extra cases of asthma (41.5%) compared with the reference group (born at ≥40 weeks gestation) were associated with delivery after 37 weeks gestation (**Table V**).

Our results confirm the association between preterm delivery and asthma in offspring and show that the magnitude of the risk decrease depends on gestational age at birth. It is well known that children born before 32 gestation weeks have a significantly higher prevalence of asthma compared with the general population.¹⁵ However, a novel finding is that the risk is still almost double in those born late preterm and that it remains significant even in those born early term (37-38 weeks gestation) compared with children born at term. We also found that 2 common risk factors for asthma, maternal asthma and male sex, were more significant in the children born term, and of minor significance in those born preterm.

Placental, uterine, fetal, and maternal conditions such as placenta previa, preeclampsia, and small for gestational age status may lead to delivery before full term.¹⁶ Other risk factors for preterm birth include maternal obesity, maternal health problems, and advanced maternal age.¹⁷ Two of 3 (66.7%) of the children with asthma were born after 39 weeks gestation, even though the incidence of asthma was lowest in this group. Had we extended gestational age at birth from 37-38 to 39 weeks, the prevalence of asthma might have dropped from 6.0% to 5.6% in this population.

Our findings also suggest that delivery after 41 weeks might have a modest protective effect against asthma compared with delivery at term. No previously published studies have suggested a similar effect, and we have no

Table IV. aORs (95% CIs) of childhood asthma after adjustment for various characteristics and risk factors

Adjusted for	Model 1	Model 2 (model 1 + maternal age and parity)*	Model A (model 2 + maternal asthma)	Model B (model 2 + smoking)	Model C (model 2 + fetal sex)	Model D (model 2 + ART)	Model E (model 2 + mode of delivery)	Model F (model 2 + maternal asthma, smoking, fetal sex, ART, and mode of delivery)
≤32 wk	4.12 (3.42-4.97)	4.31 (3.57-5.20)	4.31 (3.57-5.20)	4.51 (3.71-5.48)	4.30 (3.56-5.19)	4.20 (3.48-5.07)	4.04 (3.31-4.91)	4.10 (3.35-5.03)
33-36 wk	1.90 (1.61-2.24)	1.96 (1.66-2.32)	1.96 (1.66-2.31)	1.91 (1.60-2.27)	1.92 (1.62-2.27)	1.91 (1.62-2.26)	1.89 (1.60-2.24)	1.77 (1.48-2.11)
37-38 wk	1.34 (1.18-1.52)	1.36 (1.19-1.54)	1.35 (1.19-1.53)	1.35 (1.19-1.54)	1.33 (1.17-1.51)	1.34 (1.18-1.52)	1.33 (1.17-1.51)	1.31 (1.15-1.49)
39-40 wk	1.11 (1.00-1.23)	1.11 (1.00-1.23)	1.11 (1.00-1.23)	1.10 (0.99-1.22)	1.10 (0.99-1.22)	1.11 (1.00-1.23)	1.11 (1.00-1.23)	1.09 (0.98-1.21)
≥41 wk	1	1	1	1	1	1	1	1

Diff. cf. 2, difference compared from model 2.

*Maternal age continuous, parity (0, 1, ≥2 deliveries).

†The contribution of each factor was measured by the percentage reduction in the ORs of asthma compared with model 2 using the formula (OR model C [(A/B/C/D/E)]/OR model 2 - 1).

Table V. Burden of asthma in infants born between 1989 and 2008 at Kuopio University Hospital

Gestational age, wk	Asthma/1000 deliveries, n	Total deliveries, n	Extra cases of asthma due to prematurity, n*	Extra cases by prematurity group, n
24	216	51	8	Very preterm, 52
25	415	41	15	
26	247	73	14	
27	208	96	15	
28	245	102	20	Moderately preterm, 70
29	198	111	16	
30	100	120	6	
31	109	156	9	Late preterm, 91
32	138	218	19	
33	107	272	15	
34	100	375	18	
35	101	586	29	Early term, 108
36	78	1122	29	
37	79	2138	58	
38	61	5566	50	
39	56	10 700	43	43
≥40	52	22 446	Reference group 364	Term, late term, and postterm
		44 173		

*Extra cases of asthma among offspring because of prematurity was measured by using the formula $(n [\text{asthma}/1000 \text{ deliveries}] - n [\text{reference asthma group}] \times n [\text{total number of deliveries}]) / 1000$.

explanation for this finding. Furthermore, operative delivery, meconium-stained amniotic fluid, and maternal obesity are known to be more common in women who deliver post-term.¹⁸ These factors have been suggested to be associated with an increased incidence of allergic diseases in offspring.^{1,19,20} According to our results, however, to decrease the risk of asthma, it is advisable to avoid iatrogenic early term or late preterm delivery and to continue pregnancy as far as possible; this may be particularly important in pregnant women with asthma.

Strengths of this study include the large amount of data collected from a single university hospital with uniform data-collection criteria. Finland has high-quality national registers controlled by relevant authorities. We had the opportunity to link our birth register data to that in national registers, and thus obtained valuable and reliable information on outpatient and inpatient pharmaceutical data.

A limitation of the present study should be acknowledged. We were not able to take into account maternal stress, anxiety, and infection during labor as additional confounders for asthma in offspring. Furthermore, we had information only on the incidence of medically treated asthma, not on its severity, based on registry data. Environmental covariates after birth, such as daycare attendance, environmental tobacco smoke and pollution, and neonatal respiratory morbidity, especially in children born preterm, are potential factors for asthma in children that we were not able to control as additional confounders.

In conclusion, we found that preterm and particularly early term deliveries expose children to increased risk for

asthma. Delivery after term appears to be protective against asthma. ■

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Table II. Association between gestational age at birth and risk of asthma at any time

Gestational age, wk		Total (n = 44 173) n (%)	Asthma (n = 2661) n (%)	aOR* (95%CI)	P value
Very preterm	<24	51 (0.1)	11 (21.6)	5.6 (2.7-11.3)	.001
	25-28	312 (0.7)	80 (25.6)	6.4 (4.8-8.7)	.001
Preterm	29-32	605 (1.4)	81 (13.4)	2.9 (2.2-3.8)	.001
	33-36	2352 (5.3)	213 (9.1)	1.7 (1.4-2.0)	.001
Early term	37	2135 (4.8)	168 (7.9)	1.5 (1.2-1.8)	.001
	38	5560 (12.6)	336 (6.0)	1.2 (1.0-1.3)	.051
	39	10 699 (24.2)	598 (5.6)	1.1 (0.9-1.2)	.454
	40	12 104 (27.4)	657 (5.4)	1	
Term	41	8038 (18.2)	382 (4.8)	0.9 (0.8-1.0)	.037
Late term	41	8038 (18.2)	382 (4.8)	0.9 (0.8-1.0)	.037
Postterm	≥42	2317 (5.2)	135 (5.8)	1.0 (0.8-1.2)	.598

P values in adjusted analysis obtained from the trend test (Wald) in logistic regression models.

*Adjusted for maternal factors (asthma, diabetes mellitus, gestational diabetes mellitus, hypertension, chronic disease, age, parity, prepregnancy body mass index, smoking, marital status, and ART) and neonatal factors (sex, gestational age at birth, umbilical cord length, Apgar score at 5 minutes, mode of delivery, and number of fetuses).