


BMJ Open Natural history and associated early life factors of childhood asthma: a population registry-based cohort study in Denmark

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ABSTRACT

Objective Asthma is a common chronic disease that imposes a substantial burden on individuals and society. However, the natural history of childhood asthma in a large population remained to be studied. This study aimed to describe the natural course of childhood asthma and examine the association between early life factors and childhood asthma.

Design A population-based cohort study.

Setting This study was based on the national registry data in Denmark.

Participants All liveborn singletons in Denmark during 1995–1997 were identified and followed them till the end of 2009. Finally, 193 673 children were eligible for our study.

Exposures The following characteristics were examined as potential early life factors associated with childhood asthma, including parity, maternal asthma history, maternal smoking during pregnancy, maternal social status, delivery method and gender.

Main outcomes and measures Asthma cases were identified on the basis of hospitalisation for asthma and prescriptions for antiasthmatic medications. Asthma remission was defined as no hospitalisation or prescription recorded for 2 years. Cox proportional hazards' regression and logistic regression were used to evaluate the association between early life factors and the occurrence and remission of childhood asthma.

Results The cumulative occurrence rate of asthma in children aged 3–14 years was 13.3% and the remission rate was 44.1%. The occurrence rate decreased with age. Being female had a lower risk of asthma (HR: 0.72, 95% CI 0.70 to 0.74) and higher remission rate of asthma (HR: 1.18, 1.13 to 1.22), while maternal asthma was associated with a higher risk of asthma (HR: 2.15, 2.04 to 2.26) and decreased remission rate of asthma (HR: 0.79, 0.73 to 0.85). These patterns remained the same for early onset asthma.

Conclusions Female gender had a lower risk of asthma and a better chance of remission, while maternal asthma history had an opposite effect. The early life factors may influence the natural course of childhood asthma.

BACKGROUND

Asthma, characterised by variable respiratory symptoms and airflow limitation, is one of the most common chronic, non-communicable

Strengths and limitations of this study

- The definition of asthma was based on the registry information of the pharmacy and hospital, which was likely to be more objective.
- The present study was a longitudinal study based on the national registry databases. Therefore, selection bias would be minimised.
- However, the follow-up period was not long enough to observe asthma persistent into adulthood.

diseases in children and adults.¹ The prevalence of asthma in adults varies from 0.2% to 21.2% in different countries, while the prevalence of asthma in children ranges from 2.8% to 37.6%.² The wide range of prevalence may be in part attributable to the dynamic nature of asthma, particularly in children, and the age range of the underlying asthmatic population.

Asthmatic status is not constant across the lifecourse of the patient, and patients can experience intermittent asthma attacks.³ A Swedish prospective study recruited 3430 asthmatic children aged 7 to 8 years. After a follow-up for 11 years, 21% were in remission, 38% had periodic asthma and 41% persistent asthma at 19 years of age.⁴ In a birth cohort conducted among children who had reported wheezing in New Zealand, 27.4% had remission at 26 years old.⁵ In the Tasmanian Longitudinal Health Study, among children who reported asthma, 65% remitted after 40 years.⁶ While risk factors for childhood asthma are well studied,^{7–10} few studies have examined factors related to asthma remission.

The present study aims to examine the natural history of childhood asthma in a large population-based retrospective cohort and the association between early life risk factors and the occurrence and remission of childhood asthma in the Danish population.

Table 1 Children's and their mothers' characteristics (%)

	Non-asthma (N=167 922)	Asthma (N=25 751)	Total (N=193 673)
Maternal age at delivery, y			
<25	15.4	16.4	15.5
25–29	36.3	37.5	36.5
30–34	34.4	33.0	34.2
≥35	13.9	13.1	13.8
Parity			
1	42.7	45.2	43.0
2	37.6	37.1	37.5
≥3	19.7	17.7	19.4
Maternal socio-economic status			
Not in labour market	22.0	22.3	22.0
Unskilled workers	4.7	4.1	4.6
Skilled workers and white-collar workers	30.5	31.0	30.5
Top level status	42.0	41.9	42.0
Unknown	0.9	0.8	0.9
Maternal history of asthma			
No	96.9	93.0	96.3
Yes	3.1	7.0	3.7
Sex of the child			
Boy	50.3	58.9	51.4
Girl	49.7	41.0	48.6
Calendar year of birth			
1995	33.8	36.9	34.2
1996	32.9	33.1	32.9
1997	33.3	30.0	32.9
Maternal smoking during pregnancy			
No	69.9	66.6	69.5
Yes	24.4	27.6	24.9
Unknown	5.6	5.8	5.6
Gestational age			
22–28 weeks	0.2	0.4	0.2
29–32 weeks	0.6	0.9	0.6
33–36 weeks	3.5	4.7	3.7
37–38 weeks	14.2	15.6	14.4
39–41 weeks	71.9	69.0	71.5
42–45 weeks	9.0	8.8	9.0
Unknown	0.7	0.7	0.7
Birth weight			
<1000 g	0.1	0.3	0.1
1000–1499 g	0.3	0.6	0.4
1500–1999 g	0.7	1.0	0.7
2000–2499 g	2.1	3.0	2.2
2500–2999 g	10.2	11.1	10.3

Continued

Table 1 Continued

	Non-asthma (N=167 922)	Asthma (N=25 751)	Total (N=193 673)
3000–3499 g	31.4	30.8	31.3
3500–3999 g	34.7	33.1	34.5
4000–4499 g	15.8	15.3	15.7
4500–4999 g	3.3	3.3	3.3
≥5000 g	0.5	0.5	0.5
Unknown	1.0	1.0	1.0
Mode of delivery			
Delivered vaginally	92.2	90.8	92.0
Delivered by caesarean section	7.8	9.2	8.0
Residence			
Capital or capital suburb	27.1	25.9	26.9
Provincial city or town	12.8	13.5	12.9
Rural areas	59.2	59.8	59.3
Unknown	0.9	0.8	0.9

METHODS

Study population

Our population-based cohort study used data from the Danish Medical Birth Registry, Danish National Patient Registry and Danish National Prescription Database, linked by the unique personal identification number (assigned by the Danish Civil Registration System to all people with permanent residency in Denmark). Using the Danish Medical Birth Registry,¹¹ we identified all liveborn singletons in Denmark during 1995–1997 (N=1 97 697). We excluded 4024 children who died or emigrated before 3 years of age. Finally, 193 673 children were eligible for our study.

The information on maternal age, sex of the child, date of birth, gestational days, birth weight, parity, maternal smoking during pregnancy, mode of delivery and maternal personal identification number was obtained from the Danish Medical Birth Registry. Information on hospital contact, including hospital admission, emergency room and outpatient treatments in which asthma was the primary diagnosis, was obtained from the Danish National Patient Registry. Information on prescription of antiasthmatic medications was from the National Prescription Registry.

Covariates

Early life factors that are potentially associated with asthma were selected a priori based on the previous literature.^{12–14} They included maternal age at delivery, parity (first, second and higher), maternal socioeconomic status at delivery (not in labour market, unskilled workers, skilled workers and white-collar workers, top-level status), maternal smoking status during pregnancy (yes, no), maternal history of asthma (yes, no), sex of the

child (boy, girl), gestational weeks at delivery, maternal residence at delivery (capital or capital suburb, provincial city or town or rural areas), birth weight (an ordinal variable with every 500 g as an interval), delivery method (caesarean section (CS), coded as O82 and O842 in the 10th International Classification of Diseases, ICD-10). A directed acyclic graph is shown in online supplemental figure S1 to illustrate the association between early life determinants and childhood asthma.

Asthma definition

Wheezing is the core symptom for asthma. Diagnosing asthma in children younger than 3 years is difficult because wheezing has many causes in that age group.¹⁵ Thus, asthma was diagnosed only at 3 years of age or older. We identified childhood asthma from the Danish national registries in the 12-year period 1998–2009. Asthma cases were identified on the basis of at least one hospitalisation for asthma or two prescriptions for antiasthmatic medications, less than 12 months apart. Hospitalisation for asthma was identified based on the following the ICD-10 codes: J45, J46. The anatomical therapeutic chemical codes for inhaled antiasthmatic drugs were inhaled β_2 -agonists (R03AC02-04, R03AC12 and R03AC13), inhaled glucocorticoids (ICS; R03BA01, R03BA02 and R03BA05), fixed-dose combination of inhaled β_2 -agonists and glucocorticoids (R03AK06 and R03AK07) and leucotriene receptor antagonists (R03DC03). Two or more medications prescribed on the same day were considered to represent one prescription. The first diagnosis of asthma was defined as the date of first hospitalisation, outpatient contact or first antiasthmatic drugs redeemed in the registers in children aged 3 years or older, whichever came first. Children who did not have documented asthma based on our definition were classified as ‘non-asthmatic’.

Asthma remission was defined as no hospitalisation or prescription recorded in the following 2 years, after the last hospitalisation or prescription of antiasthmatic drugs. The date of remission was defined as 2 years after the last

asthma hospitalisation or antiasthmatic drug prescription.^{16 17} Finally, early onset asthma was defined as the first onset of asthma before 10 years old. Early remission asthma was defined as asthma remised before 12 years old.

We constructed two retrospective cohorts: asthma-onset cohort and remission cohort. The former consisted of all singleton births in 1995–1997. The age-specific and gender-specific occurrence rate of asthma was calculated as the number of newly diagnosed cases in an age-specific and gender-specific group divided by the number of children in that group. The cumulative occurrence rate of asthma was the total number of asthma cases ever diagnosed during the 12-year follow-up period to be divided by the number of children born in these 3 years. The remission cohort was composed of those who were ever been diagnosed as asthma. The remission rate was calculated as the number of children who met the criteria of asthma remission in an age-specific and gender-specific group divided by the number of children still with asthma at the beginning of that age (ie, population-at-risk of remission).

Statistical analysis

Cox proportional hazard regression model was used to examine factors that were associated with asthma onset and remission. HR with a 95% CI was estimated. In addition, logistic regression models were used to examine the association between early life factors and early onset and early remission of childhood asthma. The following variables were included in the multivariate logistic regression model, such as maternal age at delivery, maternal parity, maternal socioeconomic status at delivery, maternal smoking status during pregnancy, maternal history of asthma, sex of the child, gestational weeks at delivery, maternal residence at delivery, birth weight and delivery method. The age of asthma onset was also included in the remission analyses. All the analyses were performed

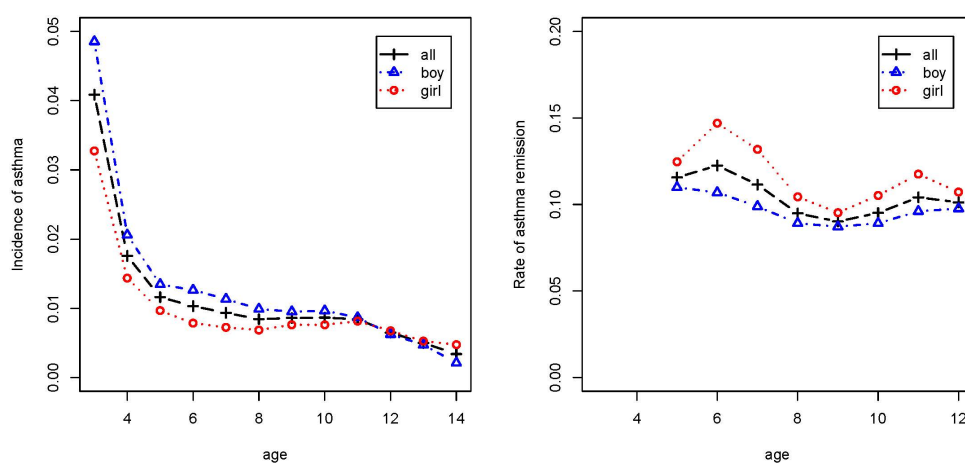


Figure 1 The incidence rate (left panel) and remission rate (right panel) of asthma by age. The x-axis is age (year), and y-axis is incidence rate (left panel) and remission rate (right panel). Black line for all children, the red line for girls and the blue line for boys.

Table 2 Prenatal factors and childhood asthma evaluated by Cox proportional hazards regression model (HR, 95% CI)

	Crude HR	95% CI	Adjusted HR*	95% CI
Maternal age	0.95	0.94 to 0.97	0.99	0.97 to 1.01
Gestational age	0.95	0.94 to 0.96	0.97	0.96 to 0.97
Birth weight	0.95	0.93 to 0.96	0.98	0.97 to 0.99
Parity				
1	Ref		Ref	
2	0.93	0.91 to 0.96	0.94	0.92 to 0.97
≥3	0.86	0.83 to 0.89	0.86	0.83 to 0.90
Maternal social status				
Not in labour market	1.06	1.03 to 1.10	1.02	0.99 to 1.06
Unskilled workers	0.92	0.86 to 0.98	0.91	0.86 to 0.98
Skilled workers and white-collar workers	1.04	1.01 to 1.07	1.00	0.97 to 1.04
Top level status	Ref		Ref	
Residence				
Capital or capital suburb	0.96	0.93 to 0.99	0.95	0.92 to 0.98
Provincial city or town	1.07	1.03 to 1.11	1.06	1.02 to 1.11
Rural areas	Ref		Ref	
Maternal smoking during pregnancy	1.16	1.13 to 1.20	1.13	1.10 to 1.16
Maternal history of asthma	2.17	2.07 to 2.28	2.15	2.04 to 2.26
Sex				
Male	Ref		Ref	
Female	0.72	0.70 to 0.74	0.72	0.70 to 0.74
Mode of delivery				
Delivered vaginally	Ref		Ref	
Delivered by caesarean section	1.19	1.14 to 1.25	1.12	1.07 to 1.17

*Cox proportional hazards regression model (HR, 95% CI) adjusting for maternal age at delivery; maternal parity; maternal socio-economic status at delivery; maternal smoking status during pregnancy; maternal history of asthma; sex of the child; gestational weeks at delivery; maternal residence at delivery; birth weight and delivery method.

using the SAS software, V.9.4 (SAS Institute, Cary, North Carolina).

RESULTS

From 1998 to 2009, 25 751 asthma cases were observed in this cohort, yielding the cumulative occurrence rate of 13.3% (95% CI 13.1% to 13.5%). Among them, 11 365 patients remised by the end of 2009, and the remission rate was 44.1% (95% CI 43.5% to 44.7%). A flowchart of subject selection in the present study is shown in online supplemental figure S2. [Table 1](#) shows demographic characteristics of the study population. Compared with children without asthma, children with asthma had a higher proportion of men (58.9% vs 50.3%). The asthma group also had a higher proportion of children delivered by CS (9.2% vs 7.8%) and maternal history of asthma (7.0% vs 3.1%), compared with children in the non-asthma group.

[Figure 1](#) shows the age-specific occurrence of asthma by gender. It ranged from 0.34% to 4.09% and decreased with age. Before 11 years old, boys had a higher occurrence rate of asthma than girls. But after that, the trend seemed reversed. The total remission rate in the study was

44%, and the age-specific rate of asthma remission ranged from 9.02% to 12.3%. The remission rate declined slightly with age. Girls had a higher remission rate than boys.

Cox proportional hazard regression model assessed the effect of early life factors on childhood asthma ([table 2](#)). Having siblings, female gender and living in capital or capital suburb would reduce the risk of asthma, while maternal smoking during pregnancy, maternal asthma history and delivered by CS would increase the risk of asthma. This risk profile is similar to that of early onset asthma ([table 3](#)).

We examined the effects of early life factors on asthma remission ([table 4](#)). Children having more siblings, middle social class, lived in capital or capital suburb, female gender, maternal smoking during pregnancy and increasing age of asthma onset had a better chance of asthma remission, while children with maternal asthma history had lower likelihood of remission.

We also explored the association of early life factors with early remission of childhood asthma ([table 5](#)). Female children, having siblings, middle social status and maternal smoking during pregnancy were associated

Table 3 Prenatal factors and early onset (<10 years of age) of childhood asthma analysed by logistic regression model in asthma patients (OR, 95% CI)

	Crude OR	95% CI	Adjusted OR*	95% CI
Maternal age	0.96	0.93 to 1.00	1.00	0.96 to 1.04
Gestational age	0.96	0.95 to 0.98	0.98	0.96 to 1.00
Birth weight	0.97	0.94 to 0.99	0.98	0.95 to 1.02
Parity				
1	Ref		Ref	
2	1.00	0.93 to 1.07	0.99	0.92 to 1.07
≥3	1.04	0.95 to 1.14	0.99	0.90 to 1.10
Maternal social status				
Not in labour market	1.32	1.22 to 1.44	1.28	1.17 to 1.40
Unskilled workers	1.38	1.17 to 1.64	1.35	1.14 to 1.60
Skilled workers and white-collar workers	1.25	1.16 to 1.35	1.21	1.12 to 1.31
Top level status	Ref		Ref	
Residence				
Capital or capital suburb	0.78	0.72 to 0.83	0.79	0.73 to 0.85
Provincial city or town	1.00	0.90 to 1.10	0.99	0.90 to 1.10
Rural areas	Ref		Ref	
Maternal smoking during pregnancy	1.10	1.03 to 1.18	1.04	0.97 to 1.12
Maternal history of asthma	1.32	1.16 to 1.61	1.32	1.15 to 1.51
Sex				
Male	Ref		Ref	
Female	0.72	0.67 to 0.76	0.71	0.67 to 0.76
Mode of delivery				
Delivered vaginally	Ref		Ref	
Delivered by caesarean section	1.25	1.11 to 1.40	1.19	1.06 to 1.34

*Logistic regression model (OR, 95% CI) adjusting for maternal age at delivery; maternal parity; maternal socio-economic status at delivery; maternal smoking status during pregnancy; maternal history of asthma; sex of the child; gestational weeks at delivery; maternal residence at delivery; birth weight and delivery method.

with a better chance of early remission of asthma. More advanced maternal age at delivery, maternal asthma history, living in middle sized cities and increasing age of asthma onset had a lower probability of early remission of asthma.

DISCUSSION

Our study is one of the largest retrospective cohort studies, showing that the overall occurrence rate of asthma in children decreased with age, with boys having a higher occurrence rate before age 11 than girls. Asthma remised in less than half of the asthmatic children by age 12–14. Girls had a higher remission rate than boys. Being a later born child, female and living in capital or capital suburb had a lower risk of asthma and a better chance of remission. Maternal asthma history increased the risk of asthma and reduced the likelihood of remission in offspring. These patterns remained the same for early-onset asthma. In addition, CS was a risk factor for early-onset asthma while the increasing gestational age at

delivery and living in capital or capital suburb was associated with a reduced risk of early-onset asthma.

The accumulative occurrence of asthma was 13.3% in our study. Previous studies from Denmark reported the prevalence of asthma ranging from 4% to 31% between 1996 and 2009. In a cross-sectional study among unselected Danish schoolchildren aged 6–17 years, the prevalence of current physician-diagnosed asthma was 4.0% in 1990–1991 and 3.6% in 2001.¹⁸ In a population-based cohort study included all live born singletons from 1996 to 2008 in northern Denmark, the prevalence of asthma was 12.4% by the end of 2009.¹⁹ In the longitudinal Danish National Birth Cohort (1996–2002), a total of 17% of children had doctor-diagnosed asthma at 18 months of age. At age 7 years, 6% of children ever had asthma with hospital admission and 31% ever with asthma medication.²⁰ The difference in the prevalence of asthma was mainly due to varying definition of asthma and the age of asthma diagnosis.^{18 19 21} The definition of asthma based on hospital contact tended to capture more severe cases, while the prescriptions of medication may identify

Table 4 Prenatal factors on childhood asthma remission evaluated by Cox proportional hazards regression model (HR, 95% CI)

	Crude HR	95% CI	Adjusted HR*	95% CI
Maternal age	0.94	0.92 to 0.96	0.93	0.91 to 0.95
Gestational age	1.00	0.99 to 1.01	1.00	0.99 to 1.01
Birth weight	0.99	0.98 to 1.01	1.00	0.99 to 1.02
Parity				
1	Ref		Ref	
2	0.98	0.94 to 1.03	1.04	0.99 to 1.08
≥3	0.99	0.94 to 1.04	1.06	1.00 to 1.13
Maternal social status				
Not in labour market	1.03	0.98 to 1.09	1.01	0.95 to 1.06
Unskilled workers	1.14	1.04 to 1.26	1.17	1.06 to 1.29
Skilled workers and white-collar workers	1.08	1.03 to 1.13	1.06	1.02 to 1.11
Top level status	Ref		Ref	
Residence				
Capital or capital suburb	1.06	1.02 to 1.11	1.07	1.02 to 1.12
Provincial city or town	0.93	0.88 to 0.99	0.95	0.89 to 1.00
Rural areas	Ref		Ref	
Maternal smoking during pregnancy	1.13	1.08 to 1.17	1.13	1.08 to 1.18
Maternal history of asthma	0.79	0.73 to 0.85	0.79	0.73 to 0.85
Sex				
Male	Ref		Ref	
Female	1.18	1.14 to 1.23	1.18	1.13 to 1.22
Mode of delivery				
Delivered vaginally	Ref		Ref	
Delivered by caesarean section	0.95	0.89 to 1.02	0.98	0.92 to 1.05
Age of asthma onset	1.10	1.09 to 1.11	1.10	1.09 to 1.11

*Cox proportional hazards regression model (HR, 95% CI) adjusting for maternal age at delivery; maternal parity; maternal socio-economic status at delivery; maternal smoking status during pregnancy; maternal history of asthma; sex of the child; gestational weeks at delivery; maternal residence at delivery; birth weight, delivery method and age of asthma onset.

a heterogeneous mix of cases from mild to severe cases.²² In order to include as many asthmatic patients as possible, we defined asthma case as at least one hospital contact for asthma or two prescriptions for asthma medication. The occurrence of asthma in our study was consistent with the previous studies in the similar study period in Denmark.²¹

The total remission rate was 44% in the present study, while the estimated remission rate varied from 22% to 65% in the literature.²³ The remission rate could be influenced by its definition, duration of follow-up and the age of the participants. Asthma remission was defined as absence of asthma symptoms and asthmatic medication use for a period of time, ranging from 1 to 10 years in different studies,^{24–29} and we defined it as the absence of asthma medication and hospitalisation in 2 years in our study.

Our results are consistent with previous studies on the effects of sex on the occurrence and remission of asthma. A cross-sectional study with 18873 participants in Italy from 1998 through 2000 found that early-onset asthma, defined as the onset before 10 years of age, occurred

more often in boys, and had a better prognosis. While late-onset asthma, generally occurring during or after puberty, more likely affected girls and had a poorer prognosis.²⁵ A similar pattern was found in Asian population.³⁰ In an unselected birth cohort conducted in Dunedin, New Zealand, 613 participants were followed from childhood to 26 years of age. More than 25% of children had persisted wheezing or relapse after remission. Girls and early onset were found to be the factors reducing asthma remission.⁵

Meanwhile, we also discovered that women had a slightly higher occurrence rate than men after 12 years of age. In the TRacking Adolescents' Individual Lives Survey, a similar shift in the prevalence of asthma occurred between 11 and 16 years. The authors attributed this crossover to both an increased incidence and decreased remission of asthma in female compared with male subjects.³¹ This phenomenon was probably owing to the onset of puberty when the increase in progesterone and oestrogen levels during the luteal phase could lead to increased inflammation of the airway wall,³² while androgens may protect

Table 5 Prenatal factors and early remission (<12 years of age) of childhood asthma analysed by logistic regression model in asthma patients (OR, 95% CI)

	Crude OR	95% CI	Adjusted OR*	95% CI
Maternal age	0.91	0.88 to 0.94	0.91	0.87 to 0.94
Gestational age	0.98	0.97 to 1.00	0.99	0.97 to 1.00
Birth weight	0.96	0.94 to 0.98	0.99	0.96 to 1.02
Parity				
1	Ref		Ref	
2	1.05	0.99 to 1.12	1.12	1.04 to 1.19
≥3	1.03	0.95 to 1.11	1.11	1.01 to 1.21
Maternal social status				
Not in labour market	1.15	1.06 to 1.24	1.06	0.98 to 1.15
Unskilled workers	1.33	1.15 to 1.54	1.30	1.12 to 1.50
Skilled workers and white-collar workers	1.27	1.19 to 1.36	1.20	1.12 to 1.28
Top level status	Ref		Ref	
Residence				
Capital or capital suburb	0.93	0.87 to 0.99	0.97	0.91 to 1.04
Provincial city or town	0.86	0.79 to 0.93	0.89	0.82 to 0.97
Rural areas	Ref		Ref	
Maternal smoking during pregnancy	1.24	1.17 to 1.32	1.19	1.12 to 1.27
Maternal history of asthma	0.80	0.71 to 0.89	0.78	0.69 to 0.87
Sex				
Male	Ref		Ref	
Female	1.20	1.13 to 1.27	1.20	1.13 to 1.27
Mode of delivery				
Delivered vaginally	Ref		Ref	
Delivered by caesarean section	1.02	0.93 to 1.12	1.01	0.91 to 1.12
Age of asthma onset	1.48	1.47 to 1.50	1.48	1.46 to 1.50

*Logistic regression model (OR, 95% CI) adjusting for maternal age at delivery; maternal parity; maternal socio-economic status at delivery; maternal smoking status during pregnancy; maternal history of asthma; sex of the child; gestational weeks at delivery; maternal residence at delivery; birth weight, delivery method and age of asthma onset.

against the development of asthma.³³ Following the population in the present study forward into adulthood would provide more understanding of the role of sex on the remission of childhood asthma.

In addition, the association of maternal asthma with childhood asthma is consistent with previous studies. The European Community Respiratory Health Survey recruited 18 156 subjects from 16 countries and found that family history of asthma or allergy was associated with a higher risk of developing asthma and a lower chance of remission.¹⁷ In the Tasmanian Longitudinal Health Study that enrolled 8583 7-year-old schoolchildren, maternal asthma was also found to adversely affect asthma remission in children.⁶ The association between maternal history and child asthma may be attributable to genetic factors and child early exposure to the same living environment.^{34 35} It was postulated that maternal asthma during pregnancy could result in decreased fetal

oxygenation during development, leading to asthma in offspring.^{36 37}

As a number of studies have demonstrated the increased risk of asthma by caesarean delivery,^{38–40} our study further showed that CS was a risk factor for early-onset asthma, and reduced the probability of asthma remission. An increased risk of asthma and asthma exacerbations was also found in the longitudinally followed COPSAC2000 birth cohort among children born by caesarean delivery.⁴¹ CS could affect the formation of normal intestinal flora of the newborn,⁴² which played an important role in the development of the immune system and, therefore, increased the risk of allergic diseases.⁴³ Anaesthetic drugs used during CS were thought to cross the placental barrier and alter the immune system of the offspring.⁴⁴ The levels of several biomarkers involved in the immune system differed significantly between CS and vaginal births, including IL-4 γ , IL-1 β , IL-6 and tumour



necrosis factor- α .^{45 46} In addition, CS was associated with offspring obesity after accounting for major confounding factors.⁴⁷ Obese asthma patients might have an increased risk of more symptoms, more frequent and severe exacerbations, reduced response to several asthma medications and decreased quality of life.⁴⁸

Consistent with the previous studies,^{49–52} maternal smoking during pregnancy increased the risk of offspring asthma. In a meta-analysis, prenatal maternal smoking was associated with a 23% increased risk of asthma between the ages of 5 and 18 years (OR=1.23, 95% CI 1.12 to 1.36, 11 studies),⁵³ which is similar to our finding. Paradoxically, maternal smoking during pregnancy was associated with an increased chance of asthma remission in offspring in our study. In the longitudinal study by Andersson *et al*, persistent asthma was also less common among children of mothers who smoked during pregnancy.⁴ A possible explanation was that maternal smoking may be more likely to cause non-allergic asthma, which remits more easily than allergic asthma.⁵⁴ The association of maternal smoking with asthma was also subjected to the ‘healthy smoker’ effect, that is, smokers are less likely to have asthma.⁵⁵ Besides, the time of maternal smoking, the number of cigarettes smoked per day, maternal home secondhand smoke exposure during pregnancy, postnatal smoke exposure and genetic factors could also impact on the effect of maternal smoking on childhood asthma. Thus, more researches would be warranted to confirm this finding.

Our study has several strengths. First, the definition of asthma was based on the registry information of the pharmacy and hospital rather than parents’ self-report. It was likely to be more objective and credible. Second, it was a longitudinal study with a very large sample size and based on the national registry database. Selection bias was minimized. However, we did not have detailed information on child growth and asthmatic symptoms. Since our study did not have information on child body mass index (BMI), we might have missed an important risk factor for asthma. It remains uncertain whether there is a causal relationship between obesity and asthma in children and adolescents.⁵⁶ Several studies have shown that obesity increased later onset of asthma, whereas others found a link only among specific subsets of at-risk patients, affected by race, sex, atopic status and timing of obesity.⁵⁷ At the meantime, several high-quality studies failed to find evidence of obesity–asthma relationship in children.⁵⁷ A US prospective cohort study showed that children with asthma had a much higher risk of developing obesity during childhood and adolescence compared with children without asthma, suggesting the possible impact of asthma history and asthma medication on the obesity risks in childhood.⁵⁸ In addition, BMI was not identified as a significant risk factor for asthma non-remission in a population-based retrospective study.¹⁴ Further research on this important factor is warranted. Besides, the follow-up period was not long enough to

observe asthma persistent into adulthood. Although the socioeconomic status (SES) data represented the status at time of delivery, it could change over time. Smoking status and asthma history of other relatives were not available in the present database. All of these may have resulted in residual confounding to an unknown degree.

CONCLUSIONS

Our study demonstrated that the overall occurrence of asthma in children decreased with age. Maternal asthma history, mode of delivery, maternal smoking during pregnancy, and sex of children affected the occurrence and remission of childhood asthma.

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