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Early View

Original research article

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Early-life risk factors for development of asthma from 8 to 28 years of age – a prospective cohort study

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Take home message: The incidence of asthma was high during childhood and the teenages but decreased substantially during young adulthood. We identified early-life risk factors for asthma in childhood, some remained important throughout the teenage years and young adulthood.

Word count: 2850

Abstract

Aim: To estimate the incidence rate of asthma from age 8 to 28 years and evaluate early-life risk factors for asthma onset at different ages.

Methods: In 1996, within the Obstructive Lung disease In Northern Sweden studies, a cohort of 3430 schoolchildren (97% of invited) was recruited at age 8y to a prospective study about asthma. The cohort was followed annually from 8-19y and at 28y by questionnaire surveys (67% of the original cohort participated). Asthma was categorized as never asthma, onset ≤8y, 9-13y, 14-19y, or >19y.

Results: Of 3430 individuals in the cohort, 690 (20.1%) reported asthma in any survey. The average incidence was 10.0/1000 per year ≤8y, 11.9/1000/y from 9 to 13y, 13.3/1000/y from 14 to 19y, and 6.1/1000/y >19y. The incidence was higher among boys until age 10y, but from age 15y, it became higher among girls. Family history of asthma, allergic sensitization, and breastfeeding <3 months were associated with asthma onset throughout the study. Low birthweight, maternal smoking during pregnancy, severe respiratory infection, rhinoconjunctivitis and eczema were associated with asthma onset ≤8y and 9 to 13y.

Conclusions: The incidence of asthma was high during childhood and the teenage period and decreased substantially during young adulthood. Early life factors were associated with asthma onset throughout childhood but had also a lasting effect on asthma incidence until adulthood.

Keywords: asthma, cohort, early origin, epidemiology, longitudinal, risk factors

Introduction

Asthma is a common disease with a particularly high incidence in childhood and the teenage years. In children and teenagers incidence rates around 6-11/1000 per year have been reported[1–4]. Also among younger adults the incidence is high, around 13/1000 per year[5], while among older adults the incidence is lower, around 2-5/1000 per year[6,7]. Among children, asthma is more common in boys than girls[4, 8–10], but in adolescence there is a gender shift, in part explained by increasing incidence among girls[3,4,10] and higher remission among boys[11].

The most important risk factors for asthma are a family history of asthma and allergic sensitization[1,9,12-15]. Other risk factors include environmental exposures, such as environmental tobacco smoke (ETS) and house dampness, and in older individuals, occupational exposures and tobacco smoking[9,12,13,16]. Several early-life risk factors have been suggested to have a long-lasting effect on asthma development, including low birth weight, short time of breastfeeding, severe respiratory infections, maternal smoking during pregnancy and postnatal ETS exposure[12,13,17-21]. Also allergic rhinitis and eczema often precedes asthma development[22,23].

However, the association between risk factors in early life and asthma has mostly been studied cross-sectionally in children or retrospectively in older ages, and are thereby subject to recall bias. There are only a few prospective studies about asthma where unselected, population-based cohorts have been followed from childhood up to adult age[8,22-26]. Consequently, studies reporting the incidence of asthma from childhood to adulthood are particularly rare. Thus, the aim of this prospective cohort study was to estimate the incidence of physician-diagnosed asthma up to 28 years of age and to study the association between early-life risk factors and asthma onset at different ages.

Material and Method

Study design and sample

The study was performed within the research program the Obstructive Lung Disease in Northern Sweden (OLIN) studies. In 1996, OLINs first pediatric cohort was recruited. The study design and recruitment procedure have been described previously[9]. In short, the parents to all children in first and second grade, aged 7-8 years (N=3525, median age 8) from

three municipalities in northern Sweden were invited to participate in a questionnaire survey. Of the invited, 97%, n=3430, participated. The cohort was followed-up annually by a questionnaire until the age of 19 years. Of the original cohort, n=2737 (79.8%) participated in at least 10 out of the 12 annual questionnaires. At age 28 years, a follow-up survey by postal questionnaire was conducted. Of the n=3245 still alive and possible to trace, n=2291 participated, constituting 71% of invited and 67% of the original cohort[25].

The Regional Ethical Review Board in Umeå, Sweden, approved the study. The parents and the participants (after they were 18 years) provided informed consent to participate in the study.

Questionnaire

At all annual surveys from 8 to 19 years of age the same questionnaire was used, the International Study of Asthma and Allergies in Childhood (ISAAC) protocol about asthma, rhinitis and eczema[27]. Additional questions about physician-diagnosis of asthma and potential risk factors such as parental smoking, respiratory infections, and birth weight were also included[28]. During the first years, the questionnaire was completed by the parents, but from 14 years of age the participants completed it themselves[29].

The follow-up at age 28 years was conducted with the OLIN questionnaire for adults, used within the OLIN studies since 1986[30] and which has been compared with other commonly used questionnaires about asthma and allergic diseases[31]. The question about physician-diagnosis of asthma was identical as in the previous annual questionnaires.

Skin prick tests

The children in two of the municipalities were invited to skin prick tests (SPT) at age 8y, 12y and 19y. Ten standard airborne allergens were included in the SPT; birch, timothy grass, mugwort, cat, dog, horse, two mites (*Dermatophagoides Farinae* and *D. Pteronyssinus*) and two molds (*Cladosporium* and *Alternaria*) (Soluprick, ALK, Hørsholm, Denmark). A positive SPT was defined as a mean wheal ≥3mm after 15 minutes to any of the ten tested allergens.

Definitions

Asthma was defined as an affirmative answer to the question “Has your child/have you been diagnosed by a physician as having asthma?” At recruitment, the reported physician-diagnosed asthma was validated through structured interviews and clinical assessments by

pediatricians[16]. Asthma at recruitment was defined as either a questionnaire report of physician-diagnosed asthma or as having asthma based on the clinical validation study[16].

Age at asthma onset was classified into mutually exclusive categories: ≤8 years: onset before age 8 years, identified at recruitment (follow-up time: 7.5 years); asthma onset 9 to 13 years (follow-up time: 5 years); asthma onset 14 to 19 years (follow-up time: 6 years) based on reports of physician-diagnosis of asthma in any of the annual questionnaire surveys. Asthma onset >19 years (follow-up time: 8.5 years) was based on reported physician-diagnosis of asthma in the follow-up at age 28y. The reference category 'never asthma' included those never reporting physician-diagnosed asthma in any of the questionnaire surveys.

Risk factors for asthma were based on parental questionnaire reports at recruitment at age 8 years and included family history of asthma, maternal smoking during pregnancy, low birthweight, breastfeeding <3 months, any severe respiratory infection, rhinoconjunctivitis, eczema, and allergic sensitization. The definitions are described in detail in Table E1 in the Online data supplement.

Statistical analyses

The computer software program SPSS, version 26.0 (IBM Corp, New York, USA) was used for analyses. The calculation of the statistical analyses are described in detail in E2, in the Online data supplement. In summary, the annual incidence rates between ages 8 to 19y was calculated based on reports of asthma in the yearly questionnaires. For onset before age 8y, the average annual incidence rate was calculated based on cases of asthma at recruitment. For onset after 19y, the average annual incidence rate was calculated based on new cases of asthma in the questionnaire at age 28y. Missing answer to the question about asthma was regarded as a negative response, while missing answers to questions about risk factors were regarded as missing and excluded from the analyses, Chi-square test were used for analysis of the association between potential risk factors and the age at asthma onset groups. A p-value of <0.05 was considered statistically significant. Significant or borderline significant risk factors ($p<0.1$) identified in the Chi-square analyses, were included in an adjusted multinomial regression analysis. The dependent variable was age at onset of asthma (categorical variable), with 'never asthma' as reference, and expressed as odds ratios (OR) with 95% confidence intervals (CI).

Results

The incidence of asthma up to 28 years of age

Throughout the observation period, n=690 (20.1%) of the entire cohort of 3430 individuals reported asthma in any of the surveys, in girls 20.8% and in boys 19.5% (p=0.338) (Table 1). Of the 690 participants with asthma, 248 (35.9%) individuals had onset of asthma ≤8y, 169 (24.5%) 9 to 13y, 184 (26.7%) 14 to 19y, and 89 (12.9%) had onset of asthma >19y of age.

The incidence rates of physician-diagnosed asthma are presented in Figure 1. The average incidence rate was 10.0/1000 per year ≤8y, 11.9/1000 per year 9 to 13y, 13.3/1000 per year 14 to 19y, and 6.1/1000 per year >19y. Until age 10y, the annual incidence rates of asthma were in general higher among boys (average 13.4/1000 per year) than girls (average 8.2/1000 per year). From age 11 to 15 years, the incidence was similar in boys and girls, and tended to be highest between 12 and 14 years of age. From 15 to 19 years of age, the incidence was higher among the girls (average 18.1/1000 per year) than boys (average 7.2/1000 per year). During young adulthood, the incidence decreased for both men and women, but was still higher among women (6.7/1000 per year) than men (5.4/1000 per year). The estimated average annual incidence rate of asthma from birth until 28 years was 8.0/1000 per year, 7.7 among men and 8.3 among women.

Risk factors in early life in relation to different ages at asthma onset

Compared with those who never reported asthma, those in any of the asthma onset categories were more likely to have a family history of asthma, low birthweight, breastfeeding<3 months, exposure to maternal smoking during pregnancy, and any severe respiratory infection before 8 years of age (Table 2). Maternal smoking during the first two years of life was slightly more common among those with asthma onset ≤8y, 9 to 13y or onset 14 to 19y compared to never physician-diagnosed asthma, but without a statistically significant association. The prevalence of rhinoconjunctivitis, eczema and allergic sensitization at age 8 years was the highest for asthma onset ≤8y and decreased by increasing age at asthma onset (Figure 2).

Risk factors related to different ages at asthma onset assessed by multinomial regression analyses

Female sex was a protective factor against asthma onset ≤8y and a risk factor for asthma onset 14 to 19y(Table 3). Family history of asthma was consistently significantly associated with all asthma categories, with the highest ORs for asthma onset ≤8y. Breastfeeding<3 months was associated with all asthma onset categories. Low birthweight, any severe respiratory infection, and eczema were associated with asthma onset ≤8y. Maternal smoking during pregnancy was associated with asthma onset 9 to 13y.

Rhinoconjunctivitis at age 8y was associated with asthma onset ≤8y and 9 to 13y. Allergic sensitization at 8y was significantly associated with all categories of age at asthma onset, with the highest OR for ≤8y. The analysis was also performed by adjusting for allergic sensitization at age 8, 12 or 19 years which yielded similar results (Table E3 in the online supplement).

Discussion

In this population-based, prospective study of asthma, in an unselected cohort of 3430 children followed from 8 until 28 years of age, we found that the incidence of asthma was highest in childhood and the teenage years and decreased in young adulthood. The incidence was higher among boys until the age of 10 years, but from 15 years, it became higher among girls. Several risk factors in early life or early childhood were still of importance for the incidence of asthma in young adulthood including short time of breastfeeding, family history of asthma and allergic sensitization, while low birthweight, maternal smoking during pregnancy, severe respiratory infections, and eczema mainly were associated with onset of asthma in childhood and adolescence. Rhinoconjuntivitis at age 8 years associated strongly with asthma development at all age at onset groups.

Until 10 years of age, the incidence of asthma varied between 9-13/1000 per year, with higher rates among boys than girls, in accordance with other studies[2,6]. After a plateau with similar asthma incidence rates, the rates increased and peaked during the early teenage years in both boys and girls. Our detailed annual examinations clearly demonstrates the shift from male to female dominance after 15 years of age. The increased incidence of asthma among girls, and higher remission rates among boys[11] contributes to the higher prevalence of asthma among women in adults[10,32].

Overall, studies on asthma incidence from childhood until young adulthood with multiple follow-ups are scarce. Both studies from the 1990s and more recent ones, including our study, show incidence rates of around 6-11/1000 per year[2,3,7,8,33]. However, comparing the incidence rate between studies is difficult for many reasons. Firstly, some of the available prospective studies recruited their participants during the 1950-70s[8,22,26] and the prevalence, treatment and awareness of asthma has changed considerably since then[32,33]. Secondly, there are different methods to calculate the incidence as it can be based either on prospective or retrospective studies[34,35] and as clearly shown in the current study, the age of the study population is of importance. Moreover, the incidence of asthma during adolescence may be underestimated if the time of baseline and endpoint measurements are too far apart[4]. Thirdly, the definition of the outcome variable may yield different results. In epidemiological studies asthma can for instance be defined based on respiratory symptoms, use of asthma medication, different measures of bronchial airflow variability or physician-diagnosis. We chose physician-diagnosed asthma as outcome as it has higher specificity compared with symptom-based variables[16]. However, this may underestimate the real incidence due to undiagnosed asthma.

Risk factors may have different impact depending on both age at exposure and age at onset of asthma. In this study, we found that the association with family history of asthma was strongest for asthma with onset in childhood, but still important for onset during theteenage years and young adulthood. This is in line with a large Danish twin study reporting that genetic factors were associated with asthma throughout the life span, while the importance of the heritability decreased with increasing age[36]. That the strength of association decreased by increasing age at asthma onset, may be a delusion effect where those most susceptible develop asthma early in life. It has been suggested that the heritability of asthma is around 60-70%[13,36] but the genetic and environmental interactions are not yet fully understood. It could be hypothesized that some gene-environment interactions are less associated with parental asthma in childhood but may become more important in adulthood due to new environmental and lifestyle exposures such as tobacco smoking and occupational exposures[12,13].

The progression of allergic diseases usually starts with development of food allergy and eczema followed by allergic sensitization. A suggested explanation would be that a defect skin barrier, skin inflammation and/or microbiome alterations could promote the development

of sensitization[37,38]. Allergic sensitization is in turn one of the strongest predictors of asthma and allergic rhinitis and usually precedes these conditions. We found that allergic sensitization at age 8y was associated with asthma onset in childhood, the teenage years as well as borderline associated with asthma in young adulthood. Moreover, we found that rhinoconjunctivitis at age 8y was associated with subsequent asthma onset, in line with other prospective studies[22,39]. Although the temporal sequence of allergic diseases was not fully investigated in the current paper, in another publication based on this cohort it was clearly shown that particularly early sensitization was strongly associated with development of both asthma and rhinitis during adolescence[40].

In line with previous studies, respiratory infections in early life was associated with asthma in childhood[12,13,20]. It has been shown that both severe symptoms of respiratory syncytial virus (RSV) and number of early respiratory infections including both RSV and rhinovirus was associated with subsequent asthma development[12,20]. Thus, primary prevention of severe respiratory infections, particularly RSV during the first years of life is important. Previous analyses of our cohort showed that respiratory infections was associated only with non-allergic asthma[16], and that infections had no impact on allergic sensitization[28], the latter in line with other studies[41,42]. Even though exclusive or prolonged breastfeeding could reduce infections and early viral wheezing[13,19], the long term effects on asthma are unclear[19,41,42]. In the current study, short time of breastfeeding was associated with asthma incidence up to young adulthood, suggesting a longterm protective effect of breastfeeding. However, the opposite has also been reported[41] indicating the complexity of the topic as sboth short time of breastfeeding and respiratory infections are more common in children with smoking mothers, which complicates the analyses.

In our study, we found that maternal smoking during pregnancy was associated with asthma, particularly with onset 9 to 13 years. It has been shown that maternal smoking during pregnancy and/or during infancy increased the risk for wheezing, asthma and had a negative effect on lung function development throughout childhood[21,24]. Moreover, smoking during pregnancy is also associated with low birthweight, which in turn is associated with asthma[17,18]. Thus, the interaction between tobacco smoke exposure, low birthweight, breastfeeding and respiratory infections may have long-term effects on lung function and asthma throughout childhood and adolescence and could partly explain the significant association between breastfeeding and onset of asthma in young adulthood in our study.

The strengths of our study are the prospective study design with long-term follow-up and high participation and retention rates throughout the study period. The change from parental to self-completed questionnaires has previously been evaluated and showed excellent agreement, especially regarding the question about physician-diagnosis of asthma[29]. A limitation was that the asthma diagnosis was not clinically verified throughout the whole observation period. However, at recruitment, the asthma diagnosis was validated showing >99 percent specificity and >70 percent sensitivity for parental reported physician-diagnosed asthma[16]. Incident asthma cases during the pre-teen and teenage period were clinically verified by spirometry with reversibility test or bronchial variability (un-published data) while cases from 19 to 28 years have not been clinically verified. Because questions about exposures in early life were completed by the parents at recruitment, the risk of recall and reporting bias was reduced. A limitation was that parental socioeconomic status was not included in any of the surveys.

In conclusion, in this prospective cohort study, we found that the incidence of asthma was high in childhood and the teenage years and decreased in young adulthood. In childhood, the incidence rates were higher among boys, but after 15 years of age higher among girls. Several early-life risk factors for asthma in childhood were identified and many of them remained important throughout the teenage years and young adulthood. Prevention of respiratory infections and environmental tobacco smoke and promotion of breastfeeding may reduce not only childhood asthma but also onset in young adulthood.

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Authorship

All authors made substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work. LH and LA drafted the manuscript, and AB, MA, HB, MSP and ER revised it critically for important intellectual content. All authors gave final approval of the version submitted for publication. All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work were appropriately investigated and resolved.

References

1. Perzanowski MS, Rönmark E, Platts-Mills TAE, et al. Effect of cat and dog ownership on sensitization and development of asthma among preteenage children. *Am J Respir Crit Care Med* 2002;166:696–702.
2. Norrman E, Nyström L, Jönsson E, et al. Prevalence and incidence of asthma and rhinoconjunctivitis in Swedish teenagers. *Allergy Eur J Allergy Clin Immunol* 1998;53:28–35.
3. Larsson L. Incidence of asthma in Swedish teenagers: Relation to sex and smoking habits. *Thorax* 1995;50:260–264.
4. Hedman L, Bjerg A, Lundbäck B, et al. Conventional epidemiology underestimates the incidence of asthma and wheeze-a longitudinal population-based study among teenagers. *Clin Transl Allergy* 2012;2:1.
5. Stern DA, Morgan WJ, Halonen M, et al. Wheezing and bronchial hyper-responsiveness in early childhood as predictors of newly diagnosed asthma in early adulthood: a longitudinal birth-cohort study. *Lancet* 2008;372:1058–1064.
6. Honkamäki J, Hisinger-Mölkänen H, Ilmarinen P, et al. Age- and gender-specific incidence of new asthma diagnosis from childhood to late adulthood. *Respir Med* 2019;154:56–62.
7. Räisänen P, Backman H, Hedman L, et al. High but stable incidence of adult-onset asthma in northern Sweden over the last decades. *ERJ Open Res* 2021;00262–02021.
8. Strachan DP, Butland BK, Anderson HR. Incidence and prognosis of asthma and wheezing illness from early childhood to age 33 in a national British cohort. *BMJ* 1996;312:1195–1199.
9. Rönmark E, Lundbäck B, Jönsson E, et al. Asthma, type-1 allergy and related conditions in 7- and 8-year-old children in Northern Sweden: Prevalence rates and risk factor pattern. *Respir Med* 1998;92:316–324.
10. Hohmann C, Keller T, Gehring U, et al. Sex-specific incidence of asthma, rhinitis and respiratory multimorbidity before and after puberty onset: Individual participant meta-

analysis of five birth cohorts collaborating in MeDALL. *BMJ Open Respir Res* 2019;6:460.

11. Andersson M, Hedman L, Bjerg A, et al. Remission and persistence of asthma followed from 7 to 19 years of age. *Pediatrics* 2013;132:435–42.

12. Scherzer R, Grayson MH. Heterogeneity and the origins of asthma. *Ann Allergy, Asthma Immunol* 2018;121:400-405.

13. Bobolea I, Arismendi E, Valero A, et al. Early life origins of asthma: A review of potential effectors. *J Investig Allergol Clin Immunol* 2019;29:168-179.

14. Rubner FJ, Jackson DJ, Evans MD, et al. Early life rhinovirus wheezing, allergic sensitization, and asthma risk at adolescence. *J Allergy Clin Immunol* 2017;139:501–507.

15. Bjerg A, Hedman L, Perzanowski MS, et al. Family history of asthma and atopy: In-depth analyses of the impact on asthma and wheeze in 7- to 8-year-old children. *Pediatrics* 2007;120:741–748.

16. Rönmark E, Jönsson E, Platts-Mills T, et al. Different pattern of risk factors for atopic and nonatopic asthma among children - Report from the obstructive lung disease in northern Sweden study. *Allergy Eur J Allergy Clin Immunol* 1999;54:926–935.

17. Bjerg A, Hedman L, Perzanowski M, et al. A strong synergism of low birth weight and prenatal smoking on asthma in schoolchildren. *Pediatrics* 2011;127:e905-912.

18. Den Dekker HT, Sonnenschein-Van Der Voort AMM, De Jongste JC, et al. Early growth characteristics and the risk of reduced lung function and asthma: A meta-analysis of 25,000 children. *J Allergy Clin Immunol* 2016;137:1026–1035.

19. Kull I, Melen E, Alm J, et al. Breast-feeding in relation to asthma, lung function, and sensitization in young schoolchildren. *J Allergy Clin Immunol* 2010;125:1013–1019.

20. Bønnelykke K, Vissing NH, Sevelsted A, et al. Association between respiratory infections in early life and later asthma is independent of virus type. *J Allergy Clin Immunol* 2015;136:81-86.e4.

21. Burke H, Leonardi-Bee J, Hashim A, et al. Prenatal and passive smoke exposure and incidence of asthma and wheeze: Systematic review and meta-analysis. *Pediatrics* 2012;129:735-744.

22. Burgess JA, Walters EH, Byrnes GB, et al. Childhood allergic rhinitis predicts asthma incidence and persistence to middle age: A longitudinal study. *J Allergy Clin Immunol* 2007;120:863–869.

23. Burgess JA, Dharmage SC, Byrnes GB, et al. Childhood eczema and asthma incidence and persistence: A cohort study from childhood to middle age. *J Allergy Clin Immunol* 2008;122:280–285.

24. Schultz ES, Hallberg J, Andersson N, et al. Early life determinants of lung function change from childhood to adolescence. *Respir Med* 2018;139:48–54.

25. Selberg S, Hedman L, Jansson SA, et al. Asthma control and acute healthcare visits among young adults with asthma—A population-based study. *J Adv Nurs* 2019;75:3525–3534.

26. Sears MR, Greene JM, Willan AR, et al. A Longitudinal, Population-Based, Cohort Study of Childhood Asthma Followed to Adulthood. *N Engl J Med* 2003;349:1414–1422.

27. Asher MI, Keil U, Anderson HR, et al. International study of asthma and allergies in childhood (ISAAC): Rationale and methods. *Eur Respir J* 1995;8:483–491.

28. Rönmark E, Bjerg A, Perzanowski M, et al. Major increase in allergic sensitization in schoolchildren from 1996 to 2006 in northern Sweden. *J Allergy Clin Immunol* 2009;124:357–363.

29. Hedman L, Lindgren B, Perzanowski M, et al. Agreement between parental and self-completed questionnaires about asthma in teenagers. *Pediatr Allergy Immunol* 2005;16:176–181.

30. Lundbäck B, Nyström L, Rosenhall L, et al. Obstructive lung disease in northern Sweden: Respiratory symptoms assessed in a postal survey. *Eur Respir J* 1991;4:257–266.

31. Ekerljung L, Rönmark E, Lötvall J, et al. Questionnaire layout and wording influence prevalence and risk estimates of respiratory symptoms in a population cohort. *Clin Respir J* 2013;7:53–63.

32. Backman H, Räisänen P, Hedman L, et al. Increased prevalence of allergic asthma from 1996 to 2006 and further to 2016—results from three population surveys. *Clin Exp Allergy* 2017;47:1426–1435.

33. Engelkes M, Janssens HM, de Ridder MAJ, et al. Time trends in the incidence, prevalence and age at diagnosis of asthma in children. *Pediatr Allergy Immunol* 2015;26:367–374.

34. Torén K, Hermansson BA. Incidence rate of adult-onset asthma in relation to age, sex, atopy and smoking: A Swedish population-based study of 15 813 adults. *Int J Tuberc Lung Dis* 1999;3:192–197.

35. Järvholm B, Brisman J, Torén K. The association between epidemiological measures of the occurrence of asthma. *Int J Tuberc Lung Dis* 1998;2:1029–1036.

36. Thomsen SF, Van Der Sluis S, Kyvik KO, et al. Estimates of asthma heritability in a large twin sample. *Clin Exp Allergy* 2010;40:1054–1061.

37. Paller AS, Spergel JM, Mina-Osorio P, et al. The atopic march and atopic multimorbidity: Many trajectories, many pathways. *J Allergy Clin Immunol* 2019;143:46–55.

38. Dharmage SC, Lowe AJ, Matheson MC, et al. Atopic dermatitis and the atopic march revisited. *Allergy* 2014;69:17-27.

39. Ballardini N, Kull I, Lind T, et al. Development and comorbidity of eczema, asthma and rhinitis to age 12 - Data from the BAMSE birth cohort. *Allergy* 2012;67:537–544.

40. Bunne J, Hedman L, Perzanowski M, et al. The majority of children sensitized before school-age develop allergic disease before adulthood: a longitudinal population-based study. *J Allergy Clin Immunol Pract* 2021;22:S2213-2198(21)01142-9.

41. Sears MR, Greene JM, Willan AR, et al. Long-term relation between breastfeeding and development of atopy and asthma in children and young adults: a longitudinal study.

Lancet 2002;360:901-7.

42. Kramer MS, Matush L, Vanilovich I, et al. Effect of prolonged and exclusive breast feeding on risk of allergy and asthma: cluster randomised trial. *BMJ* 2007;335:815.

Figure legends

Figure 1. The incidence rate of asthma up to 28 years of age. The incidence rate before 8 years, and after 19 years, respectively, are average annual estimates based on reports of asthma at age 8y and 28y, respectively. The incidence rates from 8 to 19 years are based on annual questionnaire reports of asthma.

Figure 2. The prevalence (%) of eczema, allergic sensitization and rhinoconjunctivitis at age 8 years in relation to asthma development.

Table 1. The prevalence of ever asthma* from age 8 to 28 years and distribution by age at asthma onset and sex.

	All n=3430	Girls n=1679	Boys n=1751	p-value†
Ever asthma	690 (20.1)	349 (20.8)	341 (19.5)	0.338
Age at asthma onset				
≤8 years	248 (35.9)	105 (30.1)	143 (41.9)	0.061
9 to 13 years	169 (24.5)	78 (22.3)	91 (26.7)	0.547
14 to 19 years	184 (26.7)	116 (33.2)	68 (19.9)	<0.001
>19 years	89 (12.9)	50 (14.3)	39 (11.4)	0.156

*A report of physician-diagnosed asthma in any of the questionnaire surveys

†Difference by sex analyzed by chi^2 test

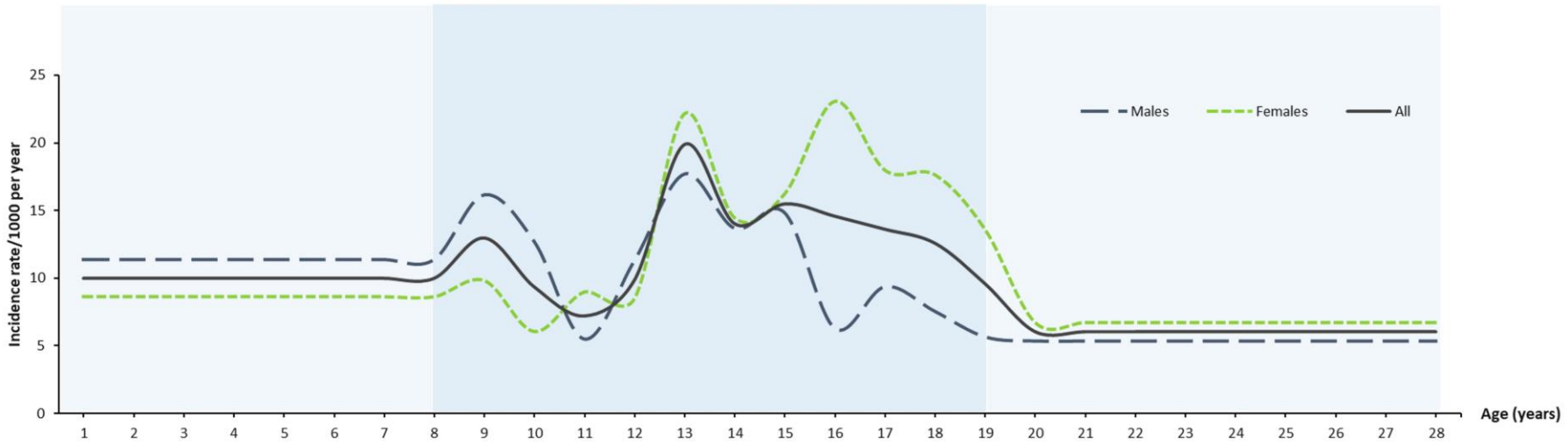
Table 2. Prevalence (%) of potential risk factors in childhood among never asthma, ever asthma and by different age at asthma onset.

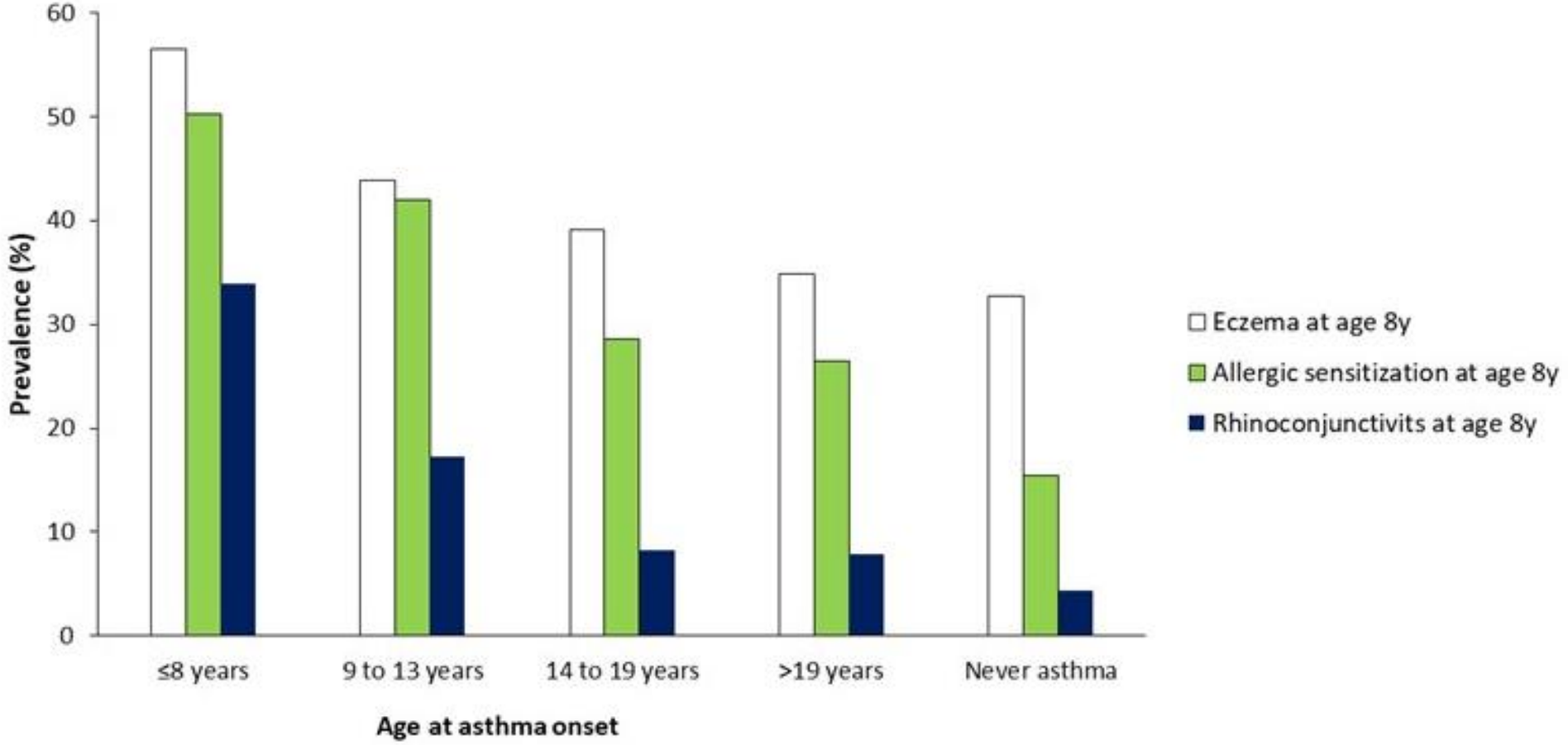
				Age at asthma onset				
	Never asthma n=2740 (%)	Ever asthma n=690 (%)	p-value*	≤8 years n=248 (%)	9 to 13 years n=169 (%)	14 to 19 years n=184 (%)	>19 years n=89 (%)	p-value†
Female sex	1330 (48.6)	349 (50.6)	0.338	105 (42.3)	78 (46.2)	116 (56.2)	50 (56.2)	<0.001
Family history of asthma	470 (17.2)	252 (36.5)	<0.001	109 (44.0)	69 (40.8)	50 (27.2)	24 (27.0)	<0.001
Low birthweight	98 (3.7)	41 (6.2)	0.004	18 (7.6)	8 (4.9)	8 (4.5)	7 (8.0)	0.019
Breastfeeding <3 months	639 (24.0)	207 (31.2)	<0.001	88 (36.7)	28 (17.2)	59 (33.5)	32 (37.6)	<0.001
Any severe respiratory infection before age 8y	1507 (55.0)	451 (65.4)	<0.001	191 (77.0)	103 (60.9)	107 (58.2)	50 (56.2)	<0.001
Smoking during pregnancy	646 (24.0)	196 (29.3)	0.005	74 (30.2)	47 (29.0)	55 (30.9)	20 (23.5)	0.043
Exposure to maternal smoking first 2y of life	816 (31.1)	228 (34.8)	0.075	85 (35.7)	53 (33.3)	64 (36.6)	26 (31.0)	0.374
Exposure to maternal smoking at age 8y	809 (30.3)	241 (36.2)	0.003	94 (39.3)	58 (35.8)	59 (33.0)	30 (35.3)	0.030

*Difference between never and ever asthma analyzed by chi^2 test.
†Difference between never asthma and all asthma onset groups analyzed by chi^2 test.
Missing values in individual variables: low birthweight n=124; breastfeeding n=104, smoking during pregnancy n=65; exposure to maternal smoking during first 2 years n=94; and exposure to maternal smoking at age 8y n=153.

Table 3. The association between risk factors in childhood and asthma by age at onset. Analyzed in a multivariable multinomial regression analysis, with 'never asthma' as reference and presented as odds ratios (OR) with 95% confidence intervals (95% CI).

	Age at asthma onset							
	≤8 years		9 to 13 years		14 to 19 years		>19 years	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Female sex	0.74	(0.54-0.99)	0.93	(0.66-1.29)	1.84	(1.33-2.56)	1.22	(0.78-1.91)
Family history of asthma	3.30	(2.43-4.48)	3.25	(2.31-4.57)	1.55	(1.08-2.24)	2.04	(1.25-3.34)
Low birthweight	1.87	(1.04-3.36)	1.24	(0.55-2.78)	1.15	(0.54-2.44)	2.12	(0.94-4.82)
Breastfeeding <3 months	2.02	(1.45-2.81)	0.63	(0.40-0.98)	1.57	(1.10-2.23)	1.75	(1.07-2.85)
Smoking during pregnancy	1.30	(0.93-1.84)	1.54	(1.05-2.25)	1.33	(0.93-1.90)	0.78	(0.45-1.35)
Any severe respiratory infection	2.76	(1.95-3.90)	1.31	(0.93-1.84)	1.11	(0.80-1.52)	1.06	(0.68-1.67)
Rhinoconjunctivits	6.55	(4.47-9.61)	2.78	(1.68-4.59)	1.48	(0.80-2.74)	1.50	(0.61-3.65)
Eczema	1.75	(1.29-2.37)	1.30	(0.93-1.83)	1.20	(0.86-1.66)	0.87	(0.53-1.41)
Allergic sensitization	3.20	(2.16-4.74)	2.92	(1.87-4.55)	2.23	(1.45-3.43)	1.95	(0.97-3.94)


Incidence rate/1000 per year
25
20
15
10
5
0
Males
Females
All
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
Age (years)


60
50
40
30
20
10
0
Prevalence (%)
≤8 years
9 to 13 years
14 to 19 years
>19 years
Never asthma
Age at asthma onset
Eczema at age 8y
Allergic sensitization at age 8y
Rhinoconjunctivits at age 8y

Online data supplement

Table E1. Definition of risk factors for asthma based on parental questionnaire reports at recruitment at age 8y

Definition	Explanation
Family history of asthma	Mother or father with asthma
Maternal smoking during pregnancy	An affirmative answer to the question "Did the mother smoke during pregnancy?"
Low birthweight	Birthweight <2500 gram
Any severe respiratory infection	A history of pertussis, croup, pneumonia or other severe respiratory infection.
Rhinoconjunctivitis	Affirmative answer to the questions "In the past 12 months, has your child had a problem with sneezing, or a runny, or a blocked nose when he/she did not have a cold or the flu?" and "In the past 12 months, has this nose problem been accompanied by itchy-watery eyes?"
Eczema	Affirmative answer to the question: "Has your child ever had eczema?"
Allergic sensitization	A positive skin prick test at age 8 years, and for an additional analysis, any positive skin prick test at age 8, 12 or 19 years.

E2. Calculations of incidence rate and early life risk factors

Incidence rate

The incidence rate was calculated as: $\frac{a}{Followup\ time \times (b-(a/2)} \times 1000$ where a is the incident cases and b the population at risk. The incident cases of asthma each year were excluded from the population at risk for the calculation of incidence rate in the next year. Non-participants in individual surveys did not contribute with person-years that specific survey.

The calculation of the average annual incidence rate from birth to 8y was based on the questionnaire survey and clinical assessment at 8y and the average follow-up time was 7.5 years. The onset of asthma was set at midpoint between birth and 8y, i.e. at 3.75 years.

The questionnaire surveys between 8 and 19 years of age were performed with yearly intervals, thus the follow-up time between each survey was one year. The onset of asthma was set at midpoint between surveys, 0.5 years.

We also calculated the average incidence rate for different age intervals as the mean of the yearly incidence rates.

The average incidence rate of asthma between 19 and 28y was based on the questionnaire survey at 28y and the average follow-up time was 8.5 years, thus the midpoint was 4.25 years.

Multinomial regression analysis of early life risk factors for asthma with onset at different ages

Early life risk factors for asthma with onset at different ages were analysed in an adjusted multinomial regression analysis. For the dependent variable, we used the entire cohort of 3430 individuals, even if not all contributed with data in all surveys. We chose a ‘last observation carried forward’ approach, and assumed that individuals that did not participate remained in the ‘never asthma’ category if they had not already been defined into any of the asthma categories.

Table E3. The association between risk factors in childhood and asthma by age at onset. Analyzed in a multivariable multinomial regression analysis, with 'never asthma' as reference and presented as odds ratios (OR) with 95% confidence intervals (95% CI). Allergic sensitization either at age 8y, 12y or 19y was included in the analysis.

	Age at asthma onset							
	≤8 years		9 to 13 years		14 to 19 years		>19 years	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Female sex	0.57	(0.41-0.79)	1.07	(0.78-1.47)	1.72	(1.25-2.36)	1.28	(0.82-1.99)
Family history of asthma	3.16	(2.27-4.41)	3.09	(2.23-4.27)	1.57	(1.10-2.25)	1.98	(1.22-3.20)
Low birthweight	2.07	(1.10-3.88)	1.36	(0.65-2.82)	1.07	(0.50-2.27)	2.42	(1.11-5.25)
Breastfeeding <3 months	1.97	(1.37-2.84)	0.71	(0.47-1.08)	1.65	(1.17-2.33)	1.90	(1.18-3.06)
Smoking during pregnancy	1.26	(0.86-1.84)	1.63	(1.14-2.33)	1.32	(0.93-1.87)	0.76	(0.44-1.30)
Any severe respiratory infection	2.71	(1.86-3.96)	1.42	(1.03-1.98)	1.13	(0.83-1.55)	1.02	(0.66-1.59)
Rhinoconjunctivits	5.73	(3.81-8.62)	4.02	(2.62-6.16)	1.92	(1.11-3.32)	1.82	(0.80-4.14)
Eczema	1.64	(1.18-2.29)	1.40	(1.01-1.93)	1.10	(0.80-1.53)	0.89	(0.55-1.43)
Allergic sensitization*	3.43	(2.28-5.14)	3.17	(2.15-4.67)	2.31	(1.61-3.32)	1.44	(0.84-2.45)

*Including the n=2443 that participated in skin prick test at age 8y, 12y or 19y.