

A prospective study on the association between hay fever among children and incidence of asthma in East Germany

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Abstract *Background* Aim of this study was to examine the effect of hay fever in childhood for asthma onset from childhood to adulthood in a prospective cohort of 3,199 asthma-free children, initially aged 5–13 years, which were followed for up to 12 years in East-Germany. *Methods* Crude and adjusted incidence rate ratios (IRR) of asthma onset due to hay fever at baseline were calculated by a generalized estimation equation approach accounting for person years at risk, age at study entry, parental asthma, and gender. *Results* Overall 142 incident cases of asthma were observed. Prevalence of hay fever at baseline was 4%. Crude and adjusted IRR were essentially the same and showed overall and in each age group a substantial higher risk of asthma onset due to hay fever. The adjusted IRR was 4 overall and ranged between 3 and 5 within the three age groups. Restricting the analysis to those participants, who were 17–25 years of age at the end of follow-up resulted in similar IRR. *Conclusion* Hay fever in childhood is a strong predictor of asthma onset later in life up to adulthood. The preventive potential of early and efficient treatment of allergic rhinitis to avoid asthma development needs to be investigated.

Keywords Adults · Asthma incidence · Children · Hay fever · Prospective cohort

Abbreviations

IR Incidence rate
IRR Incidence rate ratio
OR Odds ratio
PY Person years at risk

Introduction

Several epidemiological, experimental and clinical investigations attempt to link hay fever with asthma [1–9]. A lot of these studies listed in the reviews just cited report evidence for a close link between upper and lower airways disease of rhinitis and asthma. Some show concomitant occurrence in patients and populations, others reveal similarities in the nature of the patho-physiological and immunological processes involved [3]. Some report on an atopic march from early childhood dermatitis to rhinitis and concomitant or subsequent development of asthma [6]. Cross-sectional and also some longitudinal studies have been published studying whether rhinitis is a preceding risk factor for later asthma development [10–18]. However, prospective studies comprising the age range from childhood into adulthood are rare [10, 15, 19, 20]. The aim of the present study is to examine the role of hay fever in childhood regarding the development of asthma in later life from childhood up to adulthood.

Methods

Study design and study population

The Bitterfeld study was designed to study long-term effects of air pollution on health in children in industrialized areas of Bitterfeld and Hettstedt, which were characterized by

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high air pollution compared to the relatively low polluted county Zerbst serving as a control area. Details on results regarding the effects of air pollution over time are published elsewhere [21–23]. The Bitterfeld study consists of three cross-sectional studies conducted in 1992–1993, 1995–1996, and 1998–1999 in three regions of East Germany. Embedded is a cohort of three age groups followed from 1992 to 1999 in 3 years intervals and a fourth follow up 6 years later in 2004/2005 (see Fig. 1).

All school entrants, third, and sixth-grade school children, who were residents of Zerbst and Hettstedt counties, and a subgroup of children from randomly selected schools in Bitterfeld County, were invited to participate in our study. Overall response rates in 1992/1993, 1995/1996, and 1998/1999 were 89.1% (2,470/2,773), 75.2% (2,814/3,744), and 89.5% (2,767/3,092), respectively. Participants of each age group, who were asthma free at baseline, who gave information on hay fever and who had at least one follow-up, were pooled across the three different data collection periods. These 3,199 participants constitute the study population at baseline. Details on the sample sizes, the number of follow-up periods and the respective response rates are depicted in Fig. 1.

Informed consent was obtained from the parents of all participating children and for the final follow-up from children themselves, when aged ≥ 18 years. Approval of the study protocol was granted by the University of Rostock Ethics Committee.

Measurements

Asthma and hay fever measurements were obtained by reported doctor-diagnosis via standardized questionnaires. Questionnaires were filled in by mother, father, both parents, or other for all surveys, except for those adolescents in the

survey of 2004/2005, who have reached adulthood. At baseline the respective percentages were 51.4% filled in by mother, 1.6% by father, 44.9% by both parents and 2.1% by others.

Incident cases of asthma were obtained by defining any positive asthma diagnosis after the respective baseline survey as incident asthma in the initially asthma-free baseline population. Parental asthma was defined as any reported asthma of father or mother.

Statistical analysis

The crude asthma incidence rate (IR) of children with (respectively without) hay fever at baseline was calculated as sum of incident asthma cases at any of the three follow-ups among the children with (without) hay fever divided by the sum of person years at risk for incident asthma in the respective subgroup.

Crude and adjusted (age at study entry, parental asthma, gender) incidence rate ratios (IRR) of asthma onset due to hay fever at baseline were estimated by a generalized estimation equation approach [24], which accounts for the person years at risk (PY) for incident asthma by including the natural log of PY as offset term in the model. The error term distribution was specified as Poisson with the usual natural log-link for a Poisson-regression model.

All statistical analyses were performed by the statistical software package SAS 9.1.3 (SAS Institute Inc., Cary, NC, USA).

Results

Overall, 142 incident cases of asthma were observed from baseline to the end of follow-up in 2004/2005. Table 1 shows the observed fraction of incident asthma cases

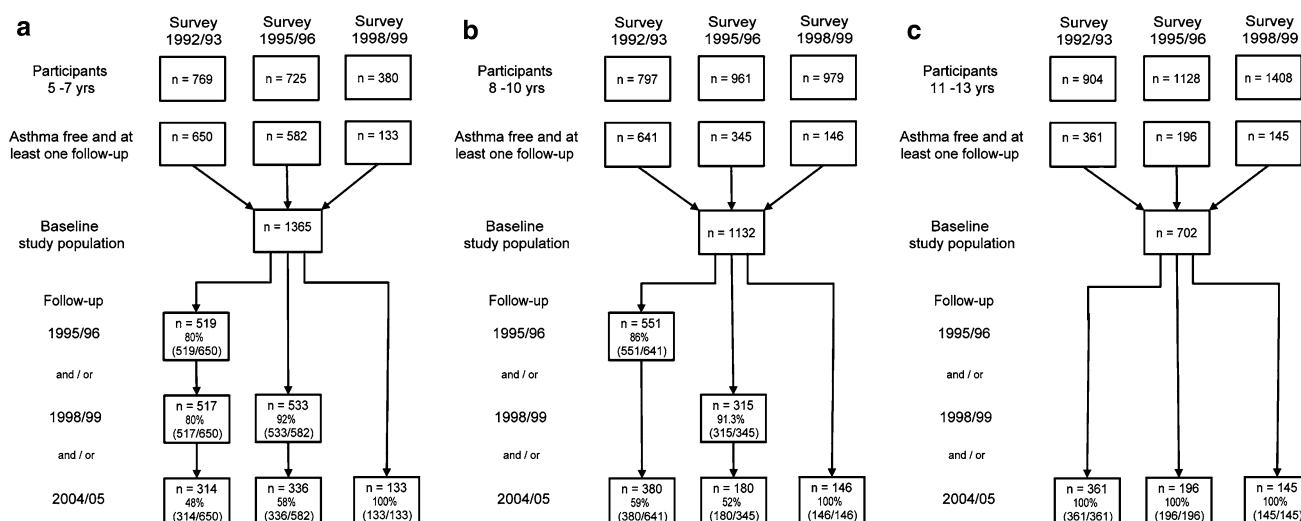


Fig. 1 Study design and study population

Table 1 Characteristics of study population at baseline and at end of follow-up

	5–7 years at baseline		8–10 years at baseline		11–13 years at baseline		All ages at baseline	
	%	(n/N)	%	(n/N)	%	(n/N)	%	(n/N)
<i>At baseline</i>								
Hay fever	2.6	(36/1,365)	4.0	(45/1,132)	6.1	(43/702)	3.9	(124/3,199)
Male gender	52.1	(711/1,365)	51.9	(587/1,132)	52.8	(371/702)	52.2	(1,669/3,199)
Parental asthma	3.9	(53/1,361)	2.3	(26/1,126)	2.7	(19/691)	3.1	(98/3,178)
Age (mean $\pm$ SD)	5.5 $\pm$ 0.51	(1,365)	8.8 $\pm$ 0.60	(1,132)	11.8 $\pm$ 0.55	(702)	8.1 $\pm$ 2.51	(3,199)
<i>From baseline to end of follow-up</i>								
Incident asthma cases	5.1	(70/1,365)	3.8	(43/1,132)	4.1	(29/702)	4.4	(142/3,199)
<i>At end of follow-up 2004/2005^a</i>								
Asthma	6.4	(50/783)	5.2	(37/706)	4.1	(29/702)	5.3	(116/2,191)
Hay fever at baseline	2.4	(19/783)	4.2	(30/706)	6.1	(43/702)	4.2	(92/2,191)
Male gender	54.8	(429/783)	51.4	(363/706)	52.8	(371/702)	53.1	(1,163/2,191)
Parental asthma	2.9	(23/780)	2.3	(16/700)	2.7	(19/691)	2.7	(58/2,171)
Age (mean $\pm$ SD)	15.7 $\pm$ 2.11	(783)	18.6 $\pm$ 1.98	(706)	21.2 $\pm$ 2.24	(702)	18.4 $\pm$ 3.12	(2,191)
Follow-up time (mean $\pm$ SD)	10.1 $\pm$ 2.15	(783)	10.1 $\pm$ 2.15	(706)	9.4 $\pm$ 2.31	(702)	9.8 $\pm$ 2.19	(2,191)
(p25, p50, p75) ^b	(9, 10, 12)		(8, 11, 11)		(8, 11, 11)		(8, 10, 12)	

^a Restricted to participants, who have information on asthma at end of follow-up in 2004/2005^b 25th, 50th (median), and 75th percentile

during follow-up for all asthma-free participants of the baseline population, who had at least one reported asthma diagnosis at any of the follow-up surveys (4.4%, all age cohorts and 5.1%, 3.8%, and 4.1% for the three age cohorts separately). Table 1 displays in addition the prevalence of hay fever and asthma and other characteristics of the study population for the three age cohorts at baseline and for those participants, who took part at the end of follow-up in 2004/2005. Both populations do not differ essentially in baseline hay fever prevalence, parental history of asthma and gender. Moreover, the mean age of the participants, who could be followed up to the end of follow-up in 2004/2005 and the average duration of follow-up time are listed.

Among all children with hay fever at baseline the overall IR was 19.88 incident asthma cases per 1,000 person years and among children without hay fever the IR was 5.03. Table 2 lists the IR and also the respective numbers of incident asthma cases and person years at risk for the three age groups. Note that the IR per 1,000 PY of children with hay fever at baseline is substantially higher in the age cohort of 5–7 years olds (31.37), than in the two older age cohorts (14.75 and 16.99).

Crude and adjusted (age at study entry, parental asthma, gender) estimated IRR for asthma onset due to preceding hay fever are depicted also in Fig. 2. Both IRR were essentially the same and showed overall and in each age group a substantial and significant higher risk of asthma

Table 2 Crude incident rates and crude and adjusted incident rate ratios of asthma onset per 1,000 person years at risk for children with and without hay fever at baseline

Cohort	Hay fever	Incident asthma cases	Person years at risk (PY)	Incidence rate (IR) per 1,000 PY	IR per 1,000 PY CI-95%	Incidence rate ratio (IRR)	IRR CI-95%	Adjusted ^a IRR	Adj. IRR CI-95%
5–7 years	Yes	8	255	31.4	16.4–60.0	5.2	2.6–10.4	4.7	2.3–9.4
	No	62	10,248	6.0	4.7–7.7				
8–10 years	Yes	5	339	14.7	6.4–33.9	3.0	1.2–7.4	3.0	1.2–8.0
	NO	38	7,799	4.9	3.6–6.5				
11–13 years	Yes	7	412	17.0	8.5–34.1	4.8	2.1–10.8	5.0	2.3–11.2
	No	22	6,219	3.5	2.3–5.3				
All ages	Yes	20	1,006	19.9	13.1–30.1	4.0	2.5–6.2	4.0	2.5–6.4
	No	122	24,266	5.0	4.2–6.0				

^a Adjusted for age at study entry, parental asthma, and gender

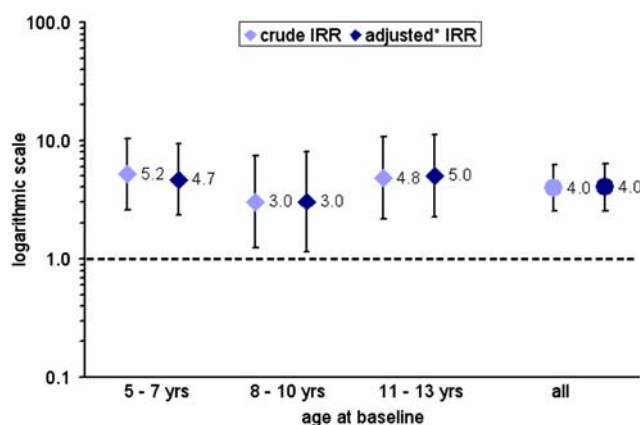


Fig. 2 Incidence rate ratios of asthma onset due to hay fever at baseline—IRR with 95%-confidence limits (semilogarithmic plot). *Adjusted for age at study entry, parental asthma and gender

onset due to hay fever. The adjusted IRR was 4.0 (2.5–6.4) overall and 4.7 (2.3–9.4), 3.0 (1.2–8.0), and 5.0 (2.3–11.2) in the respective age groups of initially 5–7 years, 8–10 years and 11–13 years old children. Restricting the analysis to those participants, who were 17–25 years of age at the end of follow-up resulted in an IRR of 4.3 (2.5–7.6) [data not shown].

Incident rate ratios for asthma onset differed, if stratified for gender. In both, the crude and in the adjusted stratified analyses, boys had lower IRR than girls, whereas this was not homogenous across the three age groups (data not shown).

Additional adjustment for exposure to environmental tobacco smoke in the first year of life, regular contact to pets, being breastfed for at least 16 weeks or active smoking did not substantially change the IRR for asthma onset for children with versus without hay fever at baseline, except for the age group of 5–7 years olds in which the IRR of asthma onset was reduced by additional adjustment for active smoking from 4.7 (2.3–9.4) to 3.7 (1.6–8.6).

Discussion

Hay fever in initially asthma free children and adolescents is a strong predictor of incident asthma in later life and young adulthood. The group of participants, who had hay fever in childhood showed a four times higher incidence rate of asthma in later life as well as in young adulthood compared to those who were not affected at start of the follow-up. Adjustment for family history of asthma, gender and age at baseline did not change these results essentially.

The few previous studies, which investigated a link between hay fever and asthma by an explicit longitudinal study design, are in line with the results of the presented analysis.

Strachan et al. 1996 estimated the association of incident wheezing illness or asthma due to hay fever from the British Birth Cohort Study comprising nearly 15,000 persons born in 1 week in 1958 for the period from 0 to 7 years, 8 to 16 years, and 17 to 33 years of age. The proportion of incident cases were 18.3, 7.9, and 24.4 incident cases per age periods between ages 0–7, 8–16, and 17–33 years, respectively. The cumulative incidence up to age 33 was 42.9. The odds ratio (OR) for the effect of hay fever on asthma incidence were 1.3, 1.4, and 1.5 for the age periods between ages 0–7, 8–16, and 17–33 years, respectively [19]. Note these associations are considerably smaller than the ones found in our study. However, they indicate as in our much smaller study a clear and significant link between hay fever and asthma incidence.

Guerra et al. [10] reported that in a nested case control study of 2,350 participants (173 asthma cases) the association of physician diagnosed asthma after the age of 20 years due to rhinitis at age 5–10 years (self-reporting to be asthma free at that time) gave an OR of 4.1 and 3.2, when adjustment for gender, years of follow-up, COPD, active smoking and atopic status were taken into account.

A further prospective population based study although comprising only partly the targeted age range in the present study followed a cohort of 734 subjects aged 15–69 year for 8 years in Copenhagen, Denmark [14]. Linneberg et al.'s results give further support to our finding of a strong predictive link between rhinitis and later asthma onset, although the study has a much smaller sample size ($n = 734$) and a wider age range than the present study.

Another longitudinal study on allergic rhinitis as a predictive factor for asthma development comprising also a wide age range (10–46 years) is a clinical study of 3,643 outpatients in an Italian clinic [15]. In this study 1,620 outpatients were diagnosed with “pure allergic rhinitis” (i.e. exclusion of asthma by bronchial provocation and physical examination) followed for treatment for 3 years. Marogna et al. reported 33% incident cases of hyper-reactivity and 18% incident cases of asthma for the “pure allergic rhinitis” group. Although these percentages are not directly comparable with our estimates of IRR they can be interpreted as consistent with the results of the present study. Also in line with the presented results is a further longitudinal clinical study on the preventive effect of specific immunotherapy on asthma onset for 142 children of 6–14 years of age with hay fever but no asthma at start of the therapy. The reported OR is 2.7 for asthma onset after 5 years of follow-up [20].

Limitations and strength

As this prospective study is not a birth cohort study we lack reliable information on (allergic) rhinitis and asthma

development before age 5 years. Consequently, our results may not be generalized to the group of early onset wheezers/asthmatics [25, 26]. For the same reason, the present study cannot really confirm or question the concept of an “atopic march” [6, 27, 28]. Pooling equivalent age cohorts from different data collection periods may be criticized as in East Germany prevalence of hay fever and asthma has increased over the last decade [29]. However, we do not think this invalidates our results. On the contrary, as hay fever prevalence may have increased in later periods averaging over different data collection periods may be considered as more conservative regarding the link of a long-term impact of hay fever on asthma incidence. Moreover, we did not find substantial changes in IRR when we included the period of data collection in the model (data not shown).

Note that there were no explicit attempts to validate the questions on reported doctor diagnoses regarding hay fever and asthma. Thus we cannot rule out completely that misclassification of exposure and disease information may have affected our results [30]. However, the questions’ formulations are orientated at the questions from the ISAAC-study questionnaires, which showed valid results in various validation studies [31].

The present study has several strengths as well. Except Strachan et al.’s and Guerra et al.’s studies this is the only prospective population-based cohort study, which analyzes the predictive link between hay fever and asthma onset from childhood into adulthood from age 5 to 13 years on up to adulthood [10, 19]. With the exception of two longitudinal clinical studies analyzing the topic with children from 6 years on [20] or 10 years on [15] and one population-based study with adolescents from 15 years on [14] all longitudinal studies were conducted in adult populations [12, 13, 16, 17], from birth to childhood [11, 28] or comprise just a 2 years follow up of 7- or 8-year-old children [18].

Conclusions

Hay fever in childhood and adolescence is a strong predictor of asthma onset later in life and young adulthood. Suggesting a common causal pathway of both diseases, further important investigations should include analyses of therapeutic potentials. The effect of early and efficient treatment of allergic rhinitis, e.g. by desensitization against certain allergens to prevent onset of asthma later in life, need to be tested in the future.

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