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Are asymptomatic airway hyperresponsiveness and allergy risk factors for asthma? A longitudinal study

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ABSTRACT: Airway hyperresponsiveness (AHR) is a characteristic feature of asthma, but it is unclear whether asymptomatic AHR is associated with a higher risk of asthma. The present study assessed whether there is an association between asymptomatic AHR in adolescence and asthma in adulthood. The association between allergy and development of asthma was also investigated.

A follow-up study of a general population cohort of adolescents was performed 14 yrs after baseline. Respiratory status was assessed at baseline in 1989 and at follow-up in 2003–2004 by a respiratory symptoms questionnaire, spirometry and histamine challenge. Allergy status was also assessed.

The respiratory status of 199 subjects was assessed twice. In total, 91 (46%) subjects had the same AHR status in combination with respiratory symptoms at follow-up as at baseline. Adjusted for age, sex, allergy, family history of asthma and smoking history, having asymptomatic AHR was not significantly related to having asthma 14 yrs later (odds ratio (OR) 2.15, 95% confidence interval (CI) 0.67–6.83). For subjects with allergy at baseline, the OR for developing asthma was 4.45 (95% CI 1.46–13.54).

Screening for asymptomatic airway hyperresponsiveness in adolescence does not identify subjects at risk of developing asthma. Conversely, the presence of allergy in adolescence does seem to be a risk factor for asthma development.

KEYWORDS: Adolescents, airway hyperresponsiveness, asthma, asymptomatic, general practice, longitudinal

Airway hyperresponsiveness (AHR) is a characteristic feature of asthma in which the airways over-respond to various stimuli, resulting in airflow obstruction [1]. AHR can be measured by means of a bronchial challenge test, usually with histamine, methacholine or adenosine 5′-monophosphate [2]. Although AHR is associated with current asthma [3], there is no complete overlap between AHR and asthma [4, 5]. Epidemiological studies have reported that 7–16% of subjects with AHR have asymptomatic AHR, *i.e.* AHR without concurrent respiratory symptoms or a medical history of asthma [4, 6–8]. It has been suggested that asymptomatic AHR is associated with a higher risk of developing asthma [9–11], with the occurrence of (irreversible) structural and functional changes in the airways [12–14]. Some studies have reported that 14–58% of subjects with initially asymptomatic AHR developed asthma in the years after this observation [9–11]. Therefore, asymptomatic AHR could be an early, pre-clinical state in the pathological process of developing asthma. BOULET [15] has suggested use of asymptomatic AHR to identify patients with a higher risk and initiate treatment to prevent the development of asthma. However, other investigators have found no evidence that asymptomatic AHR precedes symptomatic asthma [16, 17]. It is essential in this context to distinguish between *de novo* development of asthma *via* a state of asymptomatic AHR and diagnosing asthma that is as yet unrecognised by the patient and the physician, in which AHR is one of the findings supporting the diagnosis. This distinction is important for the improved understanding of the natural history of asymptomatic AHR in the general population [15]. Most studies that reported AHR to be related to the development of asthma were either based on selected populations that had been referred to specialist care, or on populations consisting of small numbers with the risk of selective inclusion [9–12]. This underlines the need to study the natural history of AHR in the

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general population in initially asthma-free, truly asymptomatic subjects.

The present study reports follow-up after 14 yrs of a cohort of adolescents recruited from the general population, with a 24% baseline prevalence of asymptomatic AHR [18–21]. The primary aim was to assess prospectively whether there is an association between asymptomatic AHR in adolescence and the development of asthma in adulthood in this cohort. The current authors also assessed whether or not the presence of allergy is associated with an increased risk of developing asthma.

METHODS

Study design and subjects

The present study was a follow-up of a cross-sectional cohort study conducted in 1989 [19–22]. The initial study group was a cohort of subjects born in 1967–1979 and registered with one of the four general practices of the Nijmegen Continuous Morbidity Registration (CMR), an academic general practice network [23]. Given the structure of the Dutch healthcare system, this cohort represents the characteristics of the Dutch population [24]. In 1989, when the subjects were aged 10–22 yrs (mean $\pm$SD 15.9 $\pm$ 3.2 yrs), all subjects were invited for a baseline assessment of their respiratory status using a respiratory symptoms questionnaire, spirometry (including reversibility testing with salbutamol), an allergy test and a histamine challenge test.

For the current study, all subjects of the initial cohort were eligible for a follow-up assessment in 2003–2004. Subjects were invited *via* a letter from their general practitioner (GP). Subjects who had moved since 1989 were traced through the general practice to their last known address. A reminder letter was sent 8 weeks after the first invitation letter.

The study was approved by the Committee on Research Involving Human Subjects of the Radboud University Nijmegen Medical Centre (Nijmegen, the Netherlands), and written informed consent was obtained from all participants.

Measurements and definitions

During the follow-up visit in 2003–2004, the respiratory status was assessed again with the same respiratory symptoms questionnaire, spirometry and histamine challenge testing.

The respiratory symptoms questionnaire was based on the children's version of the British Medical Research Council (MRC) and American Thoracic Society's respiratory symptom survey questionnaire [25] and was supplemented with questions on smoking history.

Spirometry, including reversibility testing with salbutamol, was carried out with a portable flow–volume meter (Microloop II^{TM}; MicroMedical Ltd, Rochester, UK) according to European Respiratory Society (ERS) standards [26].

Histamine challenge testing was assessed by means of the short procedure of the ERS's standardised testing procedure [27]. AHR to a nonspecific bronchoconstrictor, such as histamine, has been recommended as an objective marker of asthma-related airway lability in adolescents and young adults [28]. All challenge tests were performed by certified lung function technicians. Interpolation on a log-linear plot of histamine concentration *versus* forced expiratory volume in one second (FEV_1) was used to determine the concentration of histamine causing a 20% fall in FEV_1 (PC_{20}). When a subject reported a respiratory tract infection or worsening of symptoms in the previous 6 weeks, the test was postponed until $\geqslant$6 weeks after the end of the infection or the episode of worsened symptoms.

Baseline allergic response to common allergens had been assessed in 1989 by the Phadiatop test (Kabi Pharmacia Diagnostics AB, Uppsala, Sweden) [29]. The test was considered positive when the ratio of a subject's serum to the reference serum was >1.

Information on physician-diagnosed asthma, acute bronchitis before 1989 and family history of asthma was extracted from the medical records in the CMR practices [30]. Subjects who were unable or unwilling to take part in the study received a short *ad hoc* questionnaire, with questions regarding physician-diagnosed asthma, current medical treatment for asthma, educational level, allergy and smoking behaviour. Subjects were considered to be ''symptomatic'' at baseline and at follow-up if they reported at least one of the following symptoms: chronic cough, wheezing, chest tightness with wheezing, or breathlessness (questions 1, 4, 5 and 6 of the MRC questionnaire; table 1).

Study subjects were considered to have AHR at baseline or at follow-up if the histamine PC_{20} was $\leqslant 8.0\ mg \cdot mL^{-1}$ [26]. Subjects who had an FEV_1 value >1.64 $\times$ SD below predicted were considered to have bronchial obstruction [26, 31].

A diagnosis of asthma was assigned, in agreement with the definitions used in the 1989 study [19–22], if the subject fitted

TABLE 1 Items in the British Medical Research Council questionnaire [24] for which one or more positive responses defined subjects as ''symptomatic''

Topic	Question
Chronic cough	Did you usually, at least 5 days·week^{-1}, cough (when getting up or during the day or night) during a period of $\geqslant$3 consecutive months?
Wheezing	Have you had wheezing in your chest in the last 12 months?
Chest tightness with wheezing	Have you had attacks of tightness with wheezing in your chest (attacks of asthma) in the last 12 months?
Breathlessness	Have you had breathlessness in the last 12 months?

one or more of the following definitions: ''symptomatic'', in combination with the presence of AHR and/or bronchial obstruction with reversibility (definition 1); physician (GP or pulmonologist)-confirmed diagnosis of asthma (definition 2); and at least four recorded episodes of acute bronchitis in the CMR database prior to the baseline assessment (definition 3). In the current analysis, the third of these definitions was only used for the baseline assessment in 1989, in order to identify and exclude subjects with undiagnosed asthma in the study cohort. All other subjects were labelled ''nonasthmatic''.

A positive family history was defined as at least one first-degree relative of a participant having a physician-confirmed diagnosis of asthma. Information on family history was gathered from the CMR database [23].

Statistical analysis

Differences between participants and nonparticipants were tested using Chi-squared and one-way ANOVA tests. The main analysis was done with the data of subjects without an asthma diagnosis at baseline who were assessed at baseline and at follow-up, using a logistic regression model in which AHR and the presence or absence of respiratory symptoms at the baseline assessment were related to the diagnosis of asthma (definition 1) at the follow-up assessment. This analysis was adjusted for age, sex, allergy, positive family history of asthma, and smoking history at the time of baseline assessment. An additional analysis was performed using data from the CMR database of all subjects who had been assessed at baseline. In this analysis, the ''physician diagnosis of asthma (definition 2) since 1989'' was the dependent variable. To take into account the variable follow-up time of study subjects, Cox proportional hazards analysis was performed.

RESULTS

Study population

For the follow-up study, 468 subjects (84.9% of the baseline cohort) could be traced and were invited to take part. Figure 1 shows the flow of subjects through the study. In total, 83 subjects were lost to follow-up, of whom 77 had moved since 1989 and no current address was known. Due to significant (nonrespiratory) health problems at the time of reassessment, five subjects were excluded by their GP, and one subject had died from a nonrespiratory cause.

Out of the 468 invited subjects, 343 (73.3%) responded and 206 were willing to participate in the follow-up study. Complete follow-up data were only available for 199 subjects because seven subjects were reluctant to have the histamine challenge test. Out of the 137 subjects who were not willing to participate in the follow-up assessment, 35 completed the short *ad hoc* questionnaire.

Respiratory health status

For 199 subjects, respiratory symptoms and AHR were reassessed at follow-up. Table 2 shows the characteristics of included and not included subjects. The only statistically significant difference between these two groups was allergy status at baseline. Of the 199 subjects, 47 (23.6%) were diagnosed with asthma before or at the baseline assessment. The respiratory health reassessment of the 199 subjects

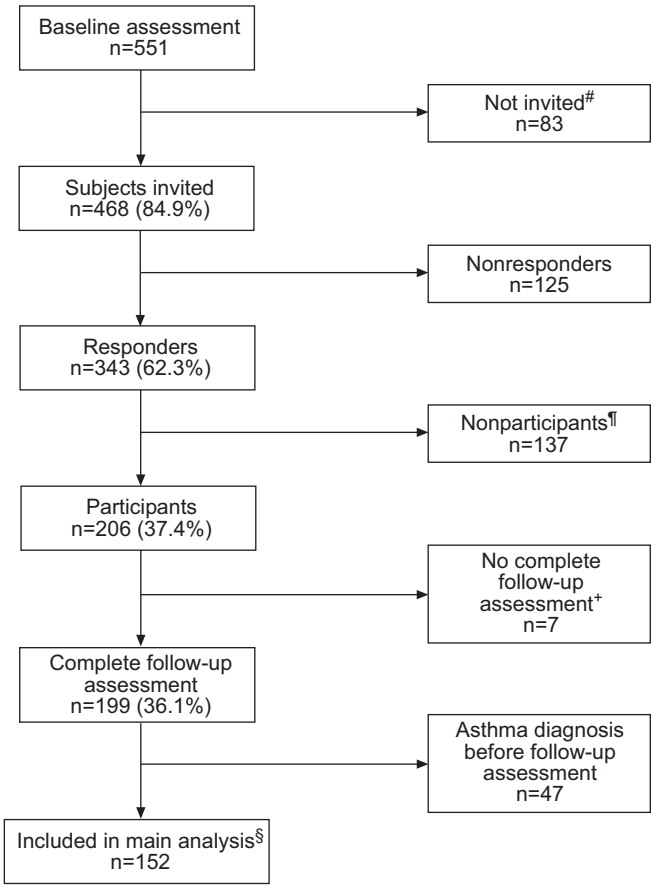

FIGURE 1. Flow of study subjects between baseline assessment in 1989 and follow-up assessment in 2003–2004. #: lost from follow-up; ¶: for 35 subjects, information was collected with a short *ad hoc* questionnaire; +: no histamine challenge test; §: for 40 subjects, baseline allergy test was missing.

revealed airflow obstruction in two (1.0%) subjects. The average FEV_1 was 100% predicted (95% confidence interval (CI) 98–102% pred). AHR (PC_{20} <8 mg·mL^{-1}) was shown by 53 (26.6%) subjects, and 87 (43.7%) subjects had respiratory symptoms at follow-up. At follow-up, the geometric mean (95% CI) of the PC_{20} of AHR subjects was 4.4 (3.7–5.0) mg·mL^{-1} histamine. Table 3 shows the presence or absence of AHR in combination with presence or absence of symptoms at the baseline assessment compared with the follow-up assessment. Of 81 subjects with AHR at baseline, 33 (40.7%) also showed AHR at follow-up, whereas of the 118 subjects without baseline AHR, 98 (83.1%) again did not show AHR at follow-up. In 1989, 47 (23.6%) subjects had shown asymptomatic AHR, with a geometric mean (95% CI) for PC_{20} of 5.6 (5.1–6.1) mg·mL^{-1}. Of these subjects, 33 had no AHR at reassessment in 2003–2004, but seven had asymptomatic AHR and another seven had symptomatic AHR. Of 199 subjects, 91 (45.7%) had the same combination of AHR status and respiratory symptoms at follow-up as at baseline.

Asthma diagnosis at follow-up

For 37 (18.5%) out of the 199 participants, the combination of symptoms and airflow obstruction and/or AHR allowed an asthma diagnosis at follow-up in 2003–2004: 31 participants

TABLE 2 Comparison between included and not included subjects for the follow-up analysis in 2003–2004

	Total	Included subjects	Not included subjects	p-value
Subjects n	551	199	352	
Males	274 (49.7)	106 (53.3)	168 (47.7)	0.21
Age yrs	29.8±3.2	30.1±3.2	29.6±3.2	0.10
Baseline assessment[#]				
Asymptomatic[¶]				
No AHR	205 (37.2)	76 (38.2)	129 (36.6)	
AHR	133 (24.1)	47 (23.6)	86 (24.4)	0.96
Symptomatic[¶]				
No AHR	114 (20.7)	42 (21.1)	72 (20.5)	
AHR[+]	99 (18.0)	34 (17.1)	65 (18.5)	
Asthma diagnosis[§]	134 (24.3)	47 (23.6)	87 (24.7)	0.77
Allergic[f]	163 (33.1)	76 (41.1)	87 (28.3)	0.004

Data are presented as n (%) or mean±SD, unless otherwise stated. AHR: airway hyperresponsiveness. [#]: in 1989; [¶]: according to questionnaire; [+]: all these subjects were classified as having asthma according to the criteria used in the present study; [§]: diagnosis by general practitioner or at baseline assessment; [f]: Phadiatop test during baseline assessment, available for 492 (89%) of the subjects in the baseline cohort.

had symptoms in combination with AHR, five participants had symptoms in combination with AHR and airflow obstruction and one participant had symptoms in combination with airflow obstruction. For 19 (9.5%) out of the 199 subjects, this was the first time asthma had been diagnosed, while the other 18 subjects had already been diagnosed with asthma before or at the baseline study. Data from the CMR database for the nonparticipants showed that GPs had diagnosed asthma in three subjects and one subject reported physician-diagnosed asthma in the short *ad hoc* questionnaire. A total of 23 new cases with asthma were identified.

TABLE 3 Presence or absence of airway hyperresponsiveness (AHR) in combination with presence or absence of symptoms at baseline compared with follow-up assessment

	Follow-up assessment[#]				
	Asymptomatic		Symptomatic		Total
	No AHR	AHR	No AHR	AHR[¶]	
Baseline assessment[+]					
Asymptomatic					
No AHR	51 (67.1)[§]	3 (3.9)	15 (19.7)	7 (9.2)	76 (100)
AHR	24 (51.1)	7 (14.9)[§]	9 (19.1)	7 (14.9)	47 (100)
Symptomatic					
No AHR	14 (33.3)	3 (7.1)	18 (42.9)[§]	7 (16.7)	42 (100)
AHR[¶]	6 (17.6)	4 (11.8)	9 (26.5)	15 (44.1)[§]	34 (100)
Total	95 (47.7)	17 (8.5)	51 (25.6)	36 (18.1)	199 (100)

Data are presented as n (%). [#]: in 2003–2004; [¶]: all these subjects were classified as having asthma according to the criteria used in the present study; [+]: in 1989; [§]: subjects with the same AHR status in combination with respiratory symptoms at baseline and follow-up.

Association between asymptomatic AHR, allergy and asthma diagnosed at follow-up

To assess whether there was an association between asymptomatic AHR in adolescence and newly diagnosed asthma (asthma definition 1) in adulthood, the final analysis was limited to the subjects without an asthma diagnosis before or at the baseline assessment (n=152; fig. 1). Of the 47 subjects with asymptomatic AHR at baseline in 1989, eight (17.0%) were classified as having asthma for the first time at follow-up in 2003–2004. Out of 76 subjects without AHR and without respiratory symptoms at baseline, seven (9.2%) were classified as having asthma at follow-up. Univariate analysis showed that this difference was not statistically significant (Chi-squared test, p=0.20). In the logistic regression analysis, this effect was adjusted for age, sex, allergy, family history of asthma and smoking history (table 4). Again, having baseline asymptomatic AHR was not a statistically significant risk factor for asthma (odds ratio (OR) 2.20, 95% CI 0.64–7.62; p=0.21; subjects without symptoms and without AHR as reference). A positive allergy test at baseline was associated with having an asthma diagnosis at follow-up (OR 4.45, 95% CI 1.46–13.54; p=0.009; negative allergy test as reference). Table 5 shows the rate of asthma diagnoses stratified by allergy status and AHR status at baseline. No statistically significant differences were found in these data. Changing the definition of AHR to <4 mg·mL^{-1} instead of <8 mg·mL^{-1} histamine did not significantly change the ORs, nor did it lead to a statistically significant difference (results not shown).

Association between asymptomatic AHR and GP-diagnosed asthma

Morbidity data from the CMR database were available for all 551 subjects of the initial study cohort, including all physician-diagnosed asthma patients. The mean±SD time of follow-up in the CMR database from the baseline assessment was 8.6±4.9 yrs. For 227 subjects there was a complete (14 yrs) follow-up in the CMR. For the Cox proportional hazards analysis, 417 subjects were available, since 134 subjects had

TABLE 4 Results of multivariate logistic regression analysis, in which airway hyperresponsiveness (AHR) and the presence or absence of respiratory symptoms at the baseline assessment were related to a new diagnosis of asthma at the follow-up assessment[#]

Covariate	OR	95% CI	p-value
Asymptomatic, AHR[¶]	2.20	0.64–7.66	0.21
Symptomatic, no AHR[¶]	2.06	0.50–8.52	0.32
Sex[+]	1.49	0.47–4.69	0.50
Positive family history[§]	0.70	0.08–6.63	0.76
Smoking in 1989	0.53	0.09–3.00	0.47
Age	0.96	0.79–1.17	0.66
Allergy[f]	4.45	1.46–13.54	0.009

The effect was adjusted for age, sex, allergy, family history of asthma and smoking history at the time of the baseline assessment; n=140. OR: odds ratio; CI: confidence interval. [#]: definition 1; [¶]: subjects without symptoms and without AHR as reference; [+]: females compared with males; [§]: at least one first-degree relative with asthma; [f]: subjects with negative Phadiatop test as reference.

TABLE 5 Breakdown of asthma diagnoses at follow-up into categories of allergy and airway hyperresponsiveness (AHR) status at baseline

	Asthma diagnosis at follow-up[#]	Subgroup total
No allergy at baseline[¶]		
Asymptomatic, no AHR	3 (6.1)	49
Asymptomatic, AHR	1 (3.8)	26
Symptomatic, no AHR	2 (12.5)	16
Total	6 (6.6)	91
Allergy at baseline[¶,+]		
Asymptomatic, no AHR	2 (11.8)	17
Asymptomatic, AHR	7 (38.9)	18
Symptomatic, no AHR	3 (21.4)	14
Total	12 (24.5)	49

Data are presented as n (%) or n. [#]: in 2003–2004, asthma definition 1; [¶]: in 1989; [+]: positive Phadiatop test. No statistically significant differences were found in these data.

already been diagnosed with asthma before (n=24) or at (n=110) the baseline assessment and these subjects were excluded from further analyses. Since the baseline assessment, seven subjects had been diagnosed with asthma by their GP for the first time (asthma definition 2), of whom four were also diagnosed with asthma at the follow-up assessment. Again, having asymptomatic AHR at baseline was not a statistically significant predictor of being assigned an asthma diagnosis by a GP compared with subjects without symptoms and without AHR (hazard ratio 1.6, 95% CI 0.4–6.5; p=0.50).

DISCUSSION

At the end of the 14-yr follow-up of study subjects, a *de novo* diagnosis of asthma was established in 23 subjects, but no relationship was found between asymptomatic AHR in adolescence and a diagnosis of asthma in adulthood. Furthermore, asymptomatic AHR turned out not to be a constant factor from adolescence to adulthood in the present general population sample, as only 46% had the same AHR status in combination with respiratory symptoms at follow-up as at baseline.

Strengths and limitations

To the current authors' knowledge, the present study is the first to investigate the relationship between asymptomatic AHR in adolescents and clinically diagnosed asthma in adulthood with the present length of follow-up and study population size. In total, 199 subjects had their respiratory status assessed twice with a time interval of 14 yrs. In addition, analysis of asymptomatic AHR in relation to physician-diagnosed asthma was possible in all 551 subjects from the 1989 study cohort, with an average follow-up of 8.6 yrs. This enabled assessment of the predictive value of asymptomatic AHR for asthma in this population.

There are, however, also some limitations to the present study. Not all subjects from the baseline assessment group could be traced. Since, at the time of the first assessment study, participants were adolescents who lived with their parents, 14 yrs later most of them had moved to live on their own and were no longer registered in their original general practices. No differences were found in age, sex or respiratory status between the study participants, the nonparticipants and the original 1989 study population, but selective participation can not be fully ruled out. Although asymptomatic AHR is thought to be associated with a higher risk for development of asthma [9–11], it is still unknown whether asymptomatic AHR precedes the development of asthma and is a risk factor preceding asthma, is a condition consistent with a very mild state of asthma that may develop into clinically more manifest asthma, or is a coincidental clinical characteristic.

Several studies have been conducted in order to elucidate the relationship between asymptomatic AHR and asthma. However, most of these studies followed their subjects for a short period of time and had smaller, selected patient samples [9–12, 16, 17, 32, 33]. LAPRISE and BOULET [11] reported a 3-yr follow-up study in 60 subjects with a mean age of 32 yrs: 30 subjects with asymptomatic AHR for methacholine and 30 normo-responsive subjects. Subjects with asymptomatic AHR had a larger increase in airway responsiveness and frequency of development of asthma symptoms than the normoresponsive subjects. Nevertheless, allergen exposure in sensitised subjects at the time of the study and genetic predisposition seemed to be the main risk factors for the development of symptomatic asthma. ZHONG *et al.* [10] reported that 20% of 50 asymptomatic students with AHR developed asthma during 2 yrs of follow-up. In contrast with these findings, the present study found that asymptomatic AHR in adolescence is not a risk factor for the development of asthma in adulthood. This is in line with DE GOOIJER *et al.* [16] and AÑÍBARRO *et al.* [17], who found no correlation between asymptomatic AHR and asthma development. AÑÍBARRO *et al.* [17] followed 15 school-aged children with rhinoconjunctivitis for 4 yrs and found that neither the presence nor the degree of AHR for methacholine

predicted development of asthma. DE GOOIJER *et al.* [16] reported that mild AHR for histamine in childhood was not a risk factor for respiratory symptoms in young adulthood. This was investigated in a 27-yr follow-up study in 60 children aged 8–11 yrs. The inconsistency of these findings regarding the relationship of AHR and asthma may be explained by differences in subject age, but may also be explained by the multicausality of AHR and asthma. AHR, as well as asthma, can probably be induced or enhanced by lower respiratory tract infections in early childhood, exposure to tobacco smoke and atopic status. For example, atopy is a known risk factor for asthma [34]. In the present study, the presence of allergy in adolescence was indeed a risk factor for the development of asthma. This suggests that the presence of allergy is more important than asymptomatic AHR when predicting future asthma.

In the present study population, AHR status was not consistent over the 14-yr observation period. This supports the view of AHR being a dynamic process that can vary over time [15, 35] rather than a static characteristic of the airways. AHR can appear or become worse after exposure to various environmental stimuli, such as exposure to tobacco smoke or the occurrence of respiratory tract infections. Conversely, AHR can also decrease, either spontaneously or after anti-inflammatory treatment. The inconsistency of AHR status in the current study subjects has probably been caused by a combination of these mechanisms. The estimate of 18.5% for the period prevalence of asthma in the cohort is quite similar to the figure of 21% that was recently reported for young adults from another Dutch birth cohort [34].

A final point that warrants discussion is the appropriateness of using histamine as a measure of AHR. Although early studies have reported that all patients with asthma are hyperreactive to histamine [3], other physiological stimuli, such as, for instance, adenosine 5′-monophosphate, may be more sensitive indicators of AHR and might have better served the purposes of the present study. However, in 1989, when the study was started, the position of adenosine was not yet established, and assessing AHR with the use of histamine was the standard in the Netherlands and across Europe. Moreover, AHR to histamine is still recommended as an objective marker of asthma-related airway lability in adolescents and young adults [28].

Clinical implications

The present study does not close the book on asymptomatic AHR as a risk factor for asthma. However, before screening for asymptomatic AHR can be recommended, it is important to have solid evidence that screening for asymptomatic AHR leads to a positive effect on the asthma burden, such as prevention of airway remodelling [36]. BOULET [15] has suggested that asymptomatic AHR could be used to identify subjects with a higher risk of developing asthma, in order to subsequently provide these patients with treatment to prevent symptoms of asthma. However, on the basis of the current study, it can be concluded that screening for asymptomatic AHR in a respiratory symptom-free population during adolescence is not likely to be a valuable action to identify subjects at risk of developing asthma. The presence of allergy in adolescence is probably a more important predictor of asthma in this respect.

Conclusion

Asymptomatic airway hyperresponsiveness in adolescence is not a risk factor for the development of asthma in adulthood. The presence of allergy in adolescence, however, seems to predict the development of asthma. Furthermore, asymptomatic airway hyperresponsiveness turned out to be an inconsistent characteristic from adolescence to adulthood after 14 yrs of follow-up. On the basis of the present study, screening for airway hyperresponsiveness in adolescents to detect subjects at risk of asthma cannot be recommended; however, in adolescents with allergy, physicians should be aware of the potentially increased risk of developing asthma while growing to maturity.

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