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AGE- AND GENDER-SPECIFIC INCIDENCE OF NEW ASTHMA DIAGNOSIS FROM CHILDHOOD TO LATE ADULTHOOD

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ABSTRACT

Background Asthma is currently divided into different phenotypes, with age at onset as a relevant differentiating factor. In addition, asthma with onset in adulthood seems to have a poorer prognosis, but studies investigating age-specific incidence of asthma with a wide age span are scarce.

Objective To evaluate incidence of asthma diagnosis at different ages and differences between child- and adult-diagnosed asthma in a large population-based study, with gender-specific analyzes included.

Methods In 2016, a respiratory questionnaire was sent to 8000 randomly selected subjects aged 20-69 years in western Finland. After two reminders, 4173 (52.3%) subjects responded. Incidence rate of asthma was retrospectively estimated based on the reported age of asthma onset. Adult-diagnosed asthma was defined as physician-diagnosis of asthma made at ≥ 18 years of age.

Results Among those with asthma, altogether, 63.7% of subjects, 58.4% of men and 67.8% of women, reported adult-diagnosed asthma. Incidence of asthma diagnosis was calculated in 10-year age groups and it peaked in young boys (0-9 years) and middle-aged women (40-49 years) and the average incidence rate during the examined period between 1946 and 2015 was 2.2/1000/year. Adult-diagnosed asthma became the dominant phenotype among asthmatics by age of 50 years and 38 years in men and women, respectively.

Conclusions Asthma is mainly diagnosed during adulthood and the incidence of asthma diagnosis peaks in middle-aged women. Asthma diagnosed in adulthood should be considered more in clinical practice and management guidelines.

INTRODUCTION

The recent re-identification of phenotypes has increased awareness of asthma as a heterogeneous disease[1,2]. Phenotypes are distinguished by age of asthma onset[1,2], and asthma with onset later in life seems to have a poorer prognosis[1,3,4]. Epidemiological factors associated with asthma and wheezing at early age are well established[5,6]. However, less is known about incidence as the examined age span is widened to late adulthood.

A substantial incidence of wheezing in childhood with a high remission rate is described by several cohort studies[6-8]. For instance, in the Tucson cohort 50% of subjects experienced at least one episode of wheezing during preschool age and 9.6% had been diagnosed with asthma at 6 years of age[9], which stands for an average incidence of physician-diagnosed asthma of 16/1000/year during preschool age. Atopy and male gender are commonly reported risk factors for wheezing in childhood[7,9-11]. After preschool age, the incidence of asthma declines[7,11,12], especially in boys[13,14].

The few longitudinal studies about adult-onset asthma have mostly reported the incidence to be 1.4-5/1000/year and higher in women[15-20]. Studies have varying age spans and the incidence in older subjects is less studied, although increasing incidence with age after mid-adulthood has been described[14,15,17]. Further, recent results from the US suggest that adult-onset asthma becomes the dominant phenotype in women quite early, at age 40 years[21], and novel data based on the entire population of Finland show similar results[13]. Nevertheless, further evidence is needed for verification of age-specific asthma incidence especially in subjects over 40 years of age. Therefore, the aim of this study was to evaluate gender-specific incidence of asthma diagnosis at different ages in a large population-based random sample of adults.

METHODS

Data acquisition

As a part of the FinEsS (Finland-Estonia-Sweden) -study, a respiratory questionnaire was sent to a random sample of 8000 subjects aged 20-69 years in western Finland (the hospital district areas of South Ostrobothnia and Vaasa, with about 200 000 and 170 000 inhabitants in 2016, respectively) in February 2016. The study area is mainly rural containing two major towns, Seinäjoki and Vaasa. Both elderly and bilinguals (Finnish and Swedish) are numerous in the population. Subjects and their personal details were identified from the Finnish Population Register, and the sample reflected age and sex distribution of the population in the study area. Up to three postal rounds were carried out or until a response was got. The registered native language of each subject determined whether questionnaire in Finnish or Swedish was applied. Subjects with other native languages were sent a Finnish questionnaire on the two first rounds and a Swedish questionnaire on the third round.

The current study was approved by the ethics committee of Helsinki University Hospital. Concurrently with this study a similar FinEsS-study was conducted in Helsinki with identical questionnaire and corresponding protocols.

Questionnaire

The FinEsS questionnaire (FQ) is developed from the Obstructive Lung Disease in Northern Sweden (OLIN) questionnaire, which is modified from the Swedish version of the British Medical Research Council (BMRC) questionnaire[22]. FQ comprises questions on respiratory symptoms and diseases, their comorbidities and suggested risk factors, use of medication and occupation, and it has been previously used in several Nordic and Estonian studies[17,23,24].

Definition of key parameters

Physician-diagnosed allergy was defined by a positive response to “Have you been diagnosed by a doctor as having allergic rhinitis caused by pollen (caused by e.g. birch, grass, mugwort)?” or “Have you been diagnosed by a doctor as having other allergic rhinitis (caused by e.g. cat or dog, but not caused by pollen)?” A positive response to “Have you been diagnosed by a doctor as having asthma?” was considered as a definition of physician-diagnosed asthma, and age at asthma diagnosis was assessed with question “What age were you when asthma was diagnosed?” Asthma diagnosed at ≥ 18 years of age was defined as adult-diagnosed asthma, and before 18 years of age as child-diagnosed asthma. A sensitivity analysis was conducted with adult-diagnosed asthma defined as asthma diagnosed at ≥ 15 years of age. Prevalence of asthma was defined as the proportion of responders reporting physician-diagnosed asthma.

Incidence of asthma diagnosis was assessed in 10-year age groups in cross-sectional data, as previously described[25]. Briefly, subjects were separated into 10-year age groups based on their current age, and “new asthma diagnoses/1000/year” was calculated by dividing the number of incident asthma diagnoses in each group by age-group-specific population at risk, dividing the result by 10 and finally multiplying with 1000.

Each 10-year age group -specific population at risk was a mean value of annually calculated respective 10-year risks. With respect to age 0, all responders were at risk. For ages 1 to 20 years, subjects reporting asthma diagnosed at younger age than the age in question were annually subtracted from the original population at risk (i.e. all responders) to form 1-year populations at risk. 20 years was the age of the youngest responders. Therefore, asthma-naïve responders younger than the age for which the population at risk was calculated were further subtracted from all responders to assess populations at risk

for ages 21-69. This subtraction procedure was applied, since responders could not have reported asthma diagnosis at older age than themselves at the time of response. Asthma-naïve responders were responders not reporting physician-diagnosed asthma. Assessing overall incidence, denominator for all diagnosed asthma cases was an average of annual populations at risk, and the result was further divided by 70, which was the length of the examined period in years. Subjects reporting physician-diagnosed asthma but not the age at diagnosis were excluded from incidence calculations.

Subjects with incomplete smoking data were included in non-responder analyses but excluded from all other analyses to allow comparison of the results with Helsinki FinEsS-data.

Statistical analyses

Statistical analyses were performed using SPSS statistics version 23 and 95% confidence intervals (CI) were calculated with EpiTools (http://epitools.ausvet.com.au) using the Wilson method, which allows CI calculation for relative proportions[26]. Percentage ranges in parentheses reflect CI. The distributions of continuous variables were evaluated, and when normally distributed, shown were mean (SD) and when non-normally distributed, shown were median (IQR). A Mann-Whitney U -test was used for continuous and chi-square -test for categorical variables to test between groups, and a p-value of < 0.05 was considered significant.

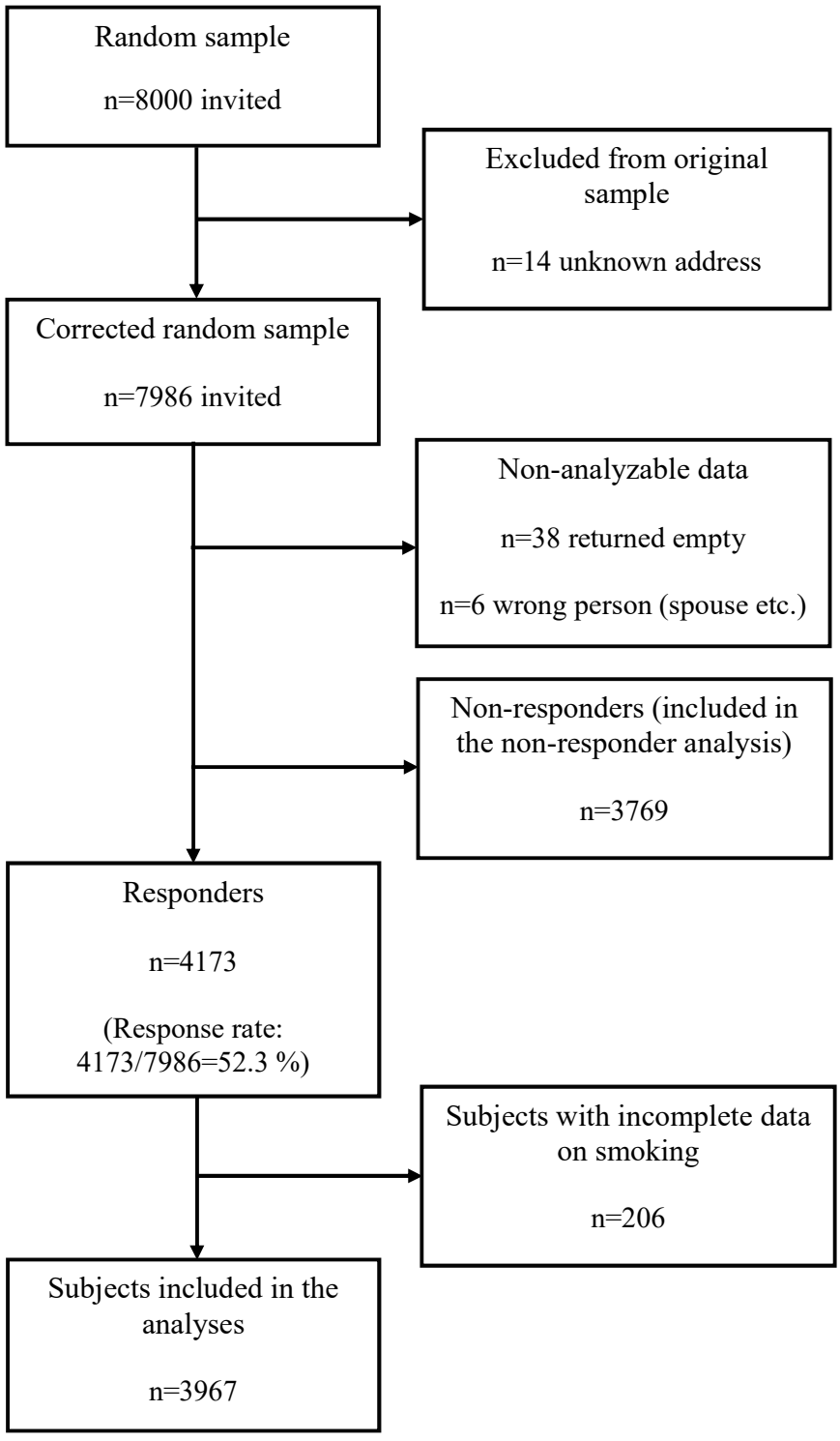

Figure 1. Flow chart of the study.

RESULTS

Characteristics of responders and prevalence of asthma

Of the 8000 invited subjects, 4173 (52.3%) responded. Median age of the responders was 53 years (Table 1). The responders were more often women (52.6% vs. 44.5%) and older (median age 53 vs. 40 years) compared to the non-responders.

Table 1. Basic characteristics of responders.

	All, N=4173		Men, N=1976		Women, N=2197	
Age (yrs), median (IQR)	53	(38-63)	54	(39-63)	53	(38-63)
BMI (kg/m^2), mean (SD)	26.7	(4.9)	27.2	(4.4)	26.3	(5.2)
Native language, n (%)						
Finnish	2932	70.3	1368	69.2	1564	71.2
Swedish	1132	27.1	554	28.0	578	26.3
Other	109	2.6	54	2.7	55	2.5
Physician-diagnosed allergy, n (%)	745	17.9	316	16.0	429	19.5
Smoking, n (%)						
Current	798	20.1	471	24.8	327	15.8
Ex	1086	27.4	635	33.5	451	21.8
Never	2083	52.5	792	41.7	1291	62.4
Family history of asthma, n (%)	1058	25.4	406	20.5	652	29.7
Physician-diagnosed chronic bronchitis or COPD, n (%)	107	2.6	59	3.0	48	2.2
Living in rural area < 5 years of age, n (%)	2859	70.1	1371	71.1	1488	69.2

BMI is based on responses of 4070 in all, 1932 in male and 2138 in female, smoking of 3967 in all, 1898 in male and 2069 in female, and rural childhood of 4080 in all, 1929 in male and 2151 in female subjects.

IQR=interquartile range, SD=standard deviation.

After exclusion of subjects with incomplete smoking data (n=206), 445 of 3967 subjects (11.2%, 10.3-12.2%) reported physician-diagnosed asthma. Further, physician-diagnosed asthma was reported by 192 of 1898 men (10.1%, 8.8-11.6%) and 253 of 2069 women (12.2%, 10.9-13.7%). 706 subjects reported physician-diagnosed allergy which resulted in prevalence of 17.8% (16.6-19.0%). Of subjects reporting physician-diagnosed asthma 88 (19.8%) were current smokers and 149 (33.5%) ex-smokers. Further, incident asthma was significantly associated with BMI in all subjects and women (Table 2 and Table 3). Smoking and BMI data in subjects categorized by age under or over 50 years was reported in detail in the Online Repository.

Table 2. Prevalence of physician-diagnosed asthma in different subgroups and comparison of responders with and without physician-diagnosed asthma.

	Prevalence of asthma in given subgroups (%) N=3967	**Responders with physician-diagnosed asthma N=445**		**Responders without physician-diagnosed asthma N=3522**		**P-value**
Age (yrs), median (IQR)	N/D	51	(35-63)	53	(38-63)	0.113
Gender, n (%)						0.035
Male	10.1	192	43.1	1706	48.4	
Female	12.2	253	56.9	1816	51.6	
BMI (kg/m^2), mean (SD)	N/D	27.4	(5.5)	26.6	(4.8)	0.020
Smoking, n (%)						0.007
Current	11.0	88	19.8	710	20.2	
Ex	13.7	149	33.5	937	26.6	
Never	10.0	208	46.7	1875	53.2	
Family history of asthma, n (%)						<0.001
Yes	20.6	208	46.7	802	22.8	
No	8.0	237	53.3	2720	77.2	
Physician-diagnosed chronic bronchitis or COPD, n (%)						<0.001
Yes	43.4	43	9.7	56	1.6	
No	10.4	402	90.3	3466	98.4	

BMI is based on responses of 3886 subjects. Gender-specific values have been calculated on the total of male and female subjects. IQR=interquartile range, SD=standard deviation.

Table 3. Gender-specific comparison of subjects in relation to physician-diagnosed asthma.

	Men N=1898		P-value	Women N=2069		P-value
	Physician-diagnosed asthma			Physician-diagnosed asthma		
	Yes N=192	No N=1706		Yes N=253	No N=1816	
Age (yrs), median (IQR)	50 (34-63)	54 (40-63)	0.806	52 (35-64)	52 (38-62)	0.040
BMI (kg/m^2), mean (SD)	27.9 (5.3)	27.1 (4.3)	0.333	27.1 (5.7)	26.2 (5.1)	0.018
Smoking, n (%)			0.156			0.007
Current	45 23.4	426 25.0		43 17.0	284 15.6	
Ex	76 39.6	559 32.8		73 28.9	378 20.8	
Never	71 37.0	721 42.3		137 54.2	1154 63.5	
Family history of asthma, n (%)	78 40.6	312 18.3	<0.001	130 51.4	490 27.0	<0.001
Physician-diagnosed chronic bronchitis or COPD n (%)	24 12.5	30 1.8	<0.001	19 7.5	26 1.4	<0.001

BMI is based on responses of 1864 subjects in men and 2022 in women. IQR=interquartile range, SD=standard deviation.

Age at diagnosis of asthma

In total, 427 subjects reporting physician-diagnosed asthma, 185 men and 242 women, reported also the age at asthma diagnosis. Median age at diagnosis was 21 (IQR 7-43) years in men and 30 (IQR 15-45) years in women (p=0.026). Altogether, 36.3% of asthmatics (31.9-41.0%) reported being diagnosed with asthma in childhood (< 18 years) and 63.7% (59.0-68.1%) in adulthood (≥ 18 years) (Figure 2). Men were diagnosed with asthma more often during childhood than women: 41.6% (34.8-48.8%) versus 32.2% (26.7-38.4%), respectively (p=0.046). Accordingly, the proportions of adult-diagnosed asthma were 58.4% (51.2-65.2%) in men, and 67.8% (61.6-73.3%) in women. A sensitivity analysis using a cut-point at 15 years also indicated prominence of adult-diagnosed asthma (see this article's Online Repository).

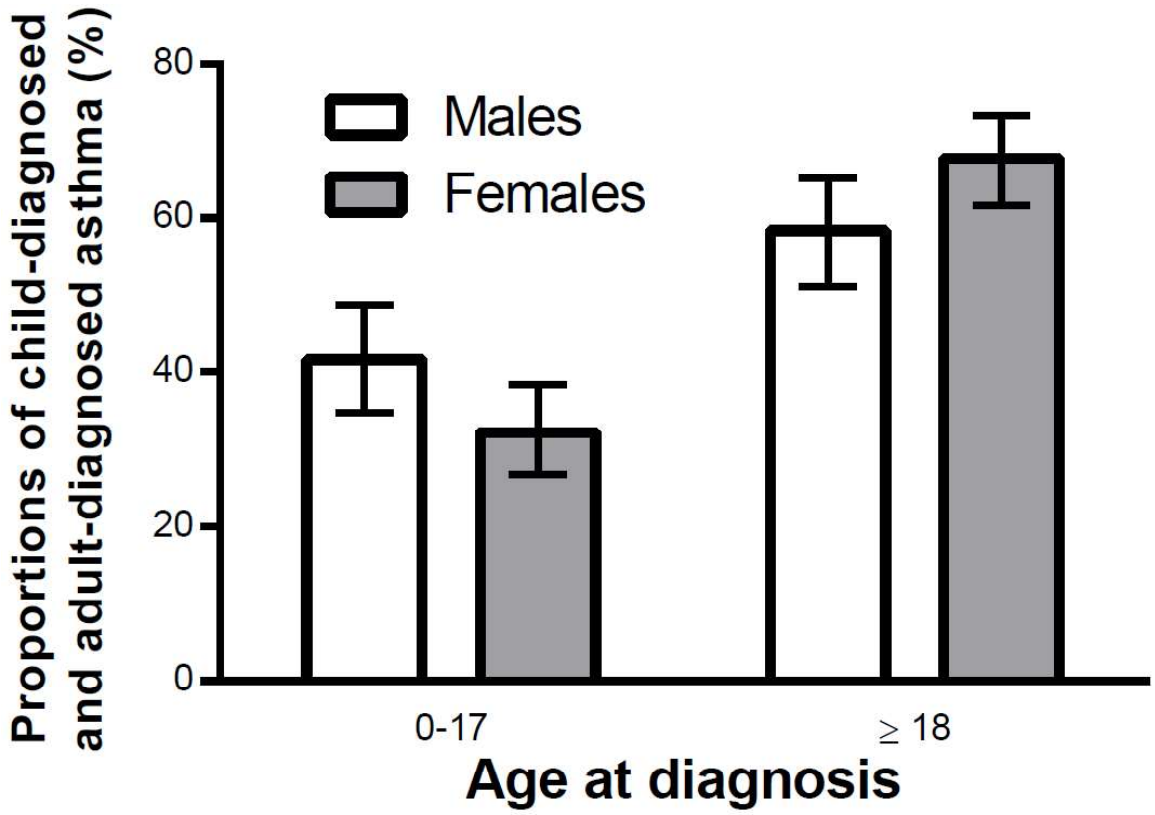

Figure 2. Gender-specific proportions of asthma diagnosed during childhood and adulthood with 95% CI:s.

After excluding subjects who reported physician-diagnosed asthma but not the age at diagnosis (n=18), incidence was calculated in 10-year age groups (Figure 3). In men, incidence peaked in childhood and was followed by a low and flat rate in adolescence and early adulthood with a slight upward trend towards late adulthood. In women, a stable trend was interrupted by a high peak in mid-adulthood (40-49 years) following a descending trend towards the oldest age group (60-69 years). On average, the incidence rate was 2.2/1000/year. Gender-specific incidence of child- and adult-diagnosed asthma are presented in Table 4. An analysis of decennial incidence of new asthma diagnosis showed increasing incidence during the whole inspected period from 1946 to 2015 (see this article´s Online Repository).

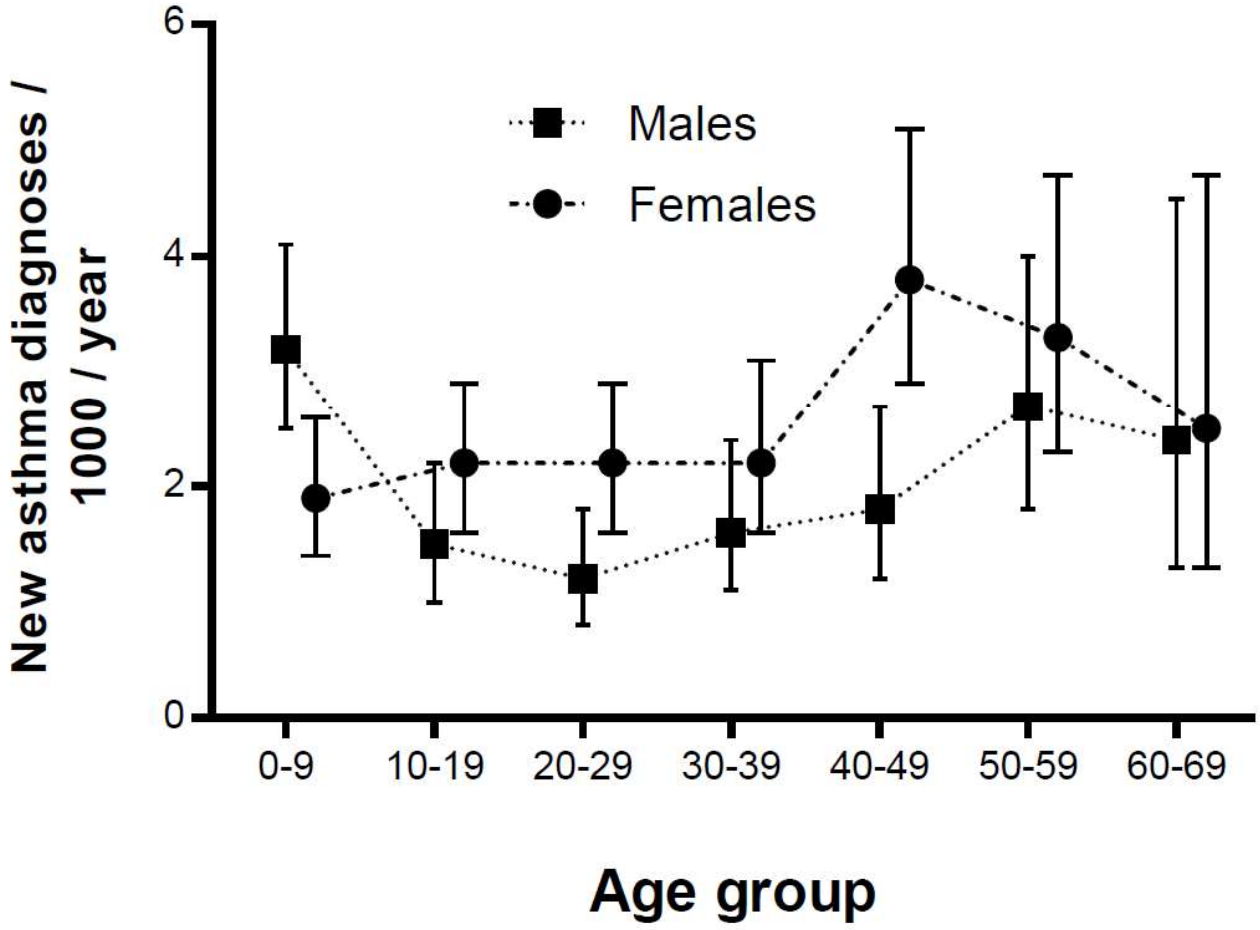

Figure 3. Age- and gender-specific incidence rates of new asthma diagnosis with 95% CI:s.

Table 4. Gender-specific incidence rates of child- and adult-diagnosed asthma.

Incidence/1000/year	All	Men	Women
Overall	2.2	2.0	2.4
Child-diagnosed (<18)	2.2	2.3	2.1
Adult-diagnosed (≥18)	2.2	1.8	2.6

The number of adult-diagnosed asthma exceeded the number of child-diagnosed asthma i.e. became the dominant phenotype in women by age 38 years and in men by age 50 years (Figure 4).

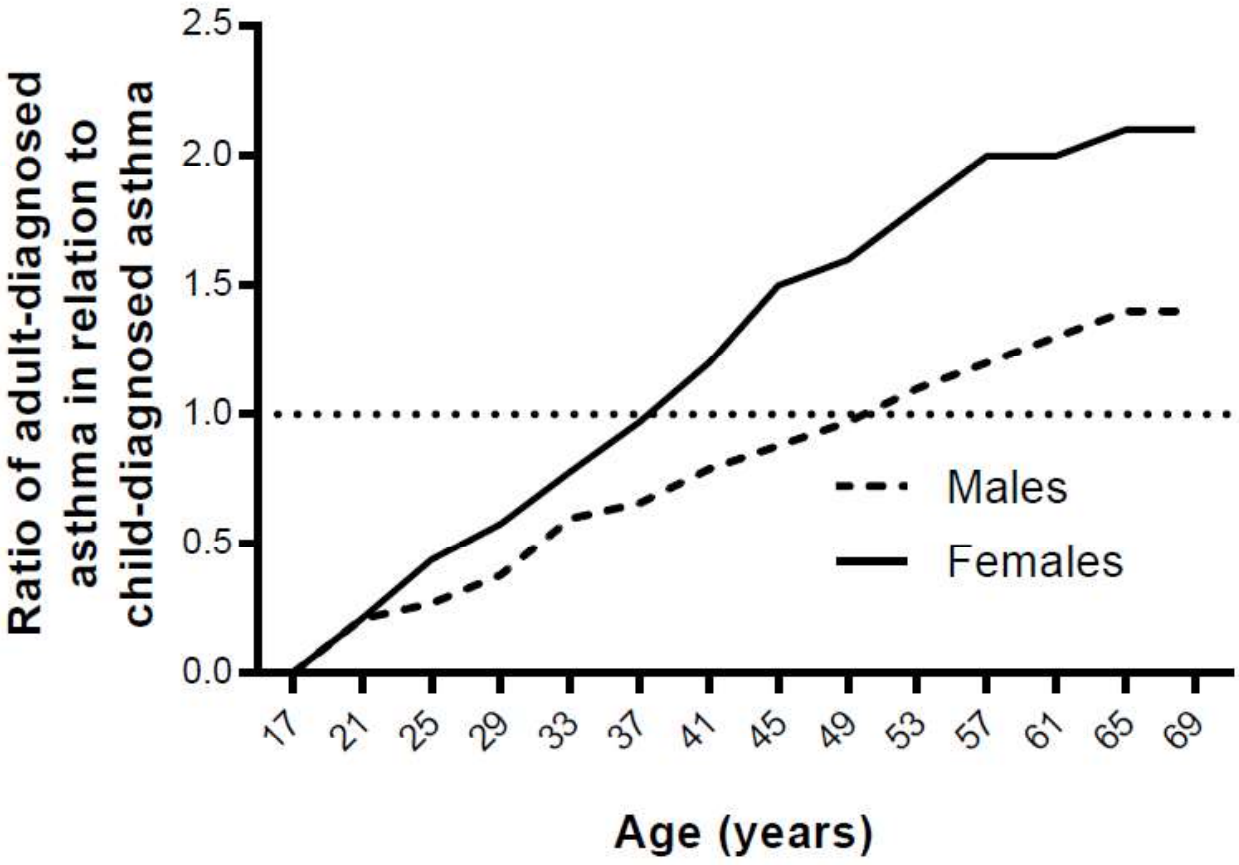

Figure 4. The ratio of adult-diagnosed asthma in relation to child-diagnosed asthma in males and females. At the age point that the curve crosses level 1, adult-diagnosed asthma becomes the dominant phenotype.

Validation of the main result

Data from Helsinki, collected with equal methods concurrently with the current study, was compared to our data from western Finland. In western Finland the proportions of child-diagnosed and adult-diagnosed asthma were 36.3% and 63.7%, respectively, as described above, and the corresponding proportions in Helsinki were 45.1% (40.2-50.0%) and 54.9% (50.0-59.8%), respectively.

DISCUSSION

In this random population sample of adults, asthma diagnosis at adult age was more common than diagnosis in childhood. The incidence peaked in young boys (0-9 years) and middle-aged women (40-49 years). Finally, adult-diagnosed asthma became the dominant phenotype by age 50 and 38 years in men and women, respectively.

Prevalence of physician-diagnosed asthma was 11.2% and is similar with novel reports from Nordic studies[27,28]. Prevalence was higher in boys than girls but higher in women than men and the gender reversal occurred in adolescence, as previously described[10,13]. The prevalence of physician-diagnosed allergy was 17.8%, and a recent Finnish study estimated it somewhat higher, but it assessed self-reported allergy[27]. Allergy prevalence varies notably between studies depending on the area and definition[29].

Incidence of asthma diagnosis in 0-18-year-old children was 2.2/1000/year, being low compared to prospective studies[6-8] which generally produce higher incidence estimates[7,12]. Reporting asthma onset is found to be less sensitive retrospectively[30,31], implying that milder asthma is left out. In addition, child-onset asthma is particularly sensitive to recall bias since in three out of four school-aged children asthma remits by mid-adulthood[6,32]. Thus, the incidence may be higher than reported here. However, our subjects reported age at asthma diagnosis which is invariably based on objective lung function testing in Finland, as the national guidelines require[13,33]. Therefore, the share of false positives is lower. In conclusion, we consider that child-diagnosed cases are reliable but represent more persistent and severe asthma, which corresponds to adult-diagnosed asthma that is less often mild[1-4].

Overall adult-diagnosed asthma incidence was 2.2/1000/year, well in line with three large adult incidence studies from Sweden performed 1985-2006 each with about 10-year

follow-up[16,19,20], and also with most other adult-onset asthma studies[15,18]. Asthma diagnosis is associated with special asthma medication reimbursement and state-funded financial benefits in Finland[13], resulting better recall of asthma diagnosis in adults. Furthermore, self-reported asthma onset reportedly has a very good specificity[30,31]. In conclusion, we consider adult-diagnosed asthma cases reliable and the number of reported diagnoses comprehensive.

Overall incidence during 1946-2015 was 2.2/1000/year in parallel to one study that reached > 50-year-old subjects[13], and another with a narrower age span but similar setting as the current study[14]. Further, age-specific incidence was higher in boys (0-9 years), equal in both genders during adolescence (10-19 years), and after that remained higher in women, also in parallel with earlier findings[10,12,13,25]. Boys are more prone to develop asthma in childhood[7,9], but persistence is associated with female gender[6,8], and sex hormones may cause susceptibility to different environmental factors[10,34]. The age- and gender-centered risk assessment seems to differentiate the patients well, and utilizing such simple characterization new asthma onset is easier to identify. This may result in less overlook and shorter delay of asthma diagnosis. Therefore, complications will be avoided and the quality of life in patients enhanced. As asthma is common in the population and over 200,000 people possessed right to asthma reimbursement in Finland in 2013[13], financial burden would consequently be significantly lessened.

Age-specific incidence rose towards late adulthood, as described earlier, but controversial results do also exist[15,18,20]. Incidence was particularly high in middle-aged women, and quite similar findings are reported[20,25]. It may be reflecting hormonal changes in mid-adulthood, such as menopause, which is recently identified as a strong predictor of asthma in women not using exogenous hormones[35]. In addition, one often reported adult-onset asthma phenotype is obesity-related, consisting more female subjects with later onset

asthma (> 40 years)[2,36]. Interestingly, BMI was also associated with the incidence of asthma in this study, in line with other Scandinavian studies[37]. Nevertheless, this phenomenon in women is significant and should be further investigated.

Proportion of adult-diagnosed asthma was higher than child-diagnosed, confirmed with Helsinki data. The result is in line with another study[13], which examined the whole age span and had an equivalent cut-point to our study (at 18 years). Since we had different aged responders and did not include subjects ≥ 70 years of age, although asthma can be found at any age[38], adult-diagnosed group lacked person-years and therefore underestimated the number of adult diagnoses. Nevertheless, our data probably underestimate the proportion of child-onset asthma and distinction between the two phenotypes might be overestimated. However, similar data for 70 years would be difficult to collect prospectively, and our data clearly describes adult-onset asthma as a notable phenomenon.

Understanding different asthma etiologies and their relative probabilities regarding age at onset in adult patients is important for physicians especially if the era of asthma phenotyping proceeds to clinical work. In our study, adult-onset asthma became the dominant phenotype in women by age 38 years, in line with two earlier reports[13,21]. A study from the US defined adult-onset asthma onset at ≥ 18 years of age, similarly to our study, whereas a Finnish study used a cut-point at 15 years[13,21]. The US study reported that child-onset asthma was still the dominant phenotype in 50-year-old men, differing from our result[21]. Averagely shorter recall periods and prospective design, leading to inclusion of mild asthma in the US study may explain the slightly different result. However, our result regarding men is in line with those of the previous Finnish study[13], which only included patients who had been granted with a special medication reimbursement, indicating that all patients had objectively diagnosed, more persistent asthma.

Smoking has been associated with asthma in incidence studies[20], while most cross-sectional studies have found association with ex-smoking[28,39], similarly to this study. This is presumably explained by the "healthy smoker effect": bias caused by smoking cessation because of excessive respiratory symptoms and asthma diagnosis[16]. In addition, asthma-COPD overlap (ACO) is recently identified[40]. Patients with asthma smoke as often as non-asthmatics and in adult asthma populations many have at least some smoking history[3,28,36,38]. In previous adult asthma studies the exclusion of current smokers or patients with smoking history might lower the incidence estimates in adults, and the influence is emphasized in women, in whom smoking is a higher risk factor for asthma onset[39]. In Finland COPD is diagnosed with objective lung function tests which serve as a basis for medication reimbursement, similarly as in asthma[13,33]. Nevertheless, we cannot exclude some misclassification between asthma and COPD, especially in elderly patients, since COPD usually occurs after 50 years of age. However, the majority of patients with asthma diagnosed > 40 years of age were women, in which significant smoking history is less common in Finland[41]. Thus, we consider that the bias due to misclassification of COPD as asthma does not explain the higher numbers of newly-diagnosed asthma in older women.

In the last three decades, over 130 birth cohorts on asthma and allergies have been initiated[5]. In contrast, similar adult cohort studies are scarce. Although some birth cohorts suggest that adult-onset asthma may have manifested in childhood[5,7], adult- and child-onset asthma have highly distinct characteristics and treatment response, implying that it may be appropriate to study them as separate entities[1,2,42]. In addition, adult-onset asthma is more often associated with environmental risk factors, implying that substantial potential for prevention exists[42]. In a clinical study with population from the same area as in the current study, 24% of adult patients with verified new-onset asthma had had asthma

symptoms in childhood[36] and a case-control study from Sweden found that approximately 10% of subjects with recently diagnosed asthma had been symptomatic before[37]. Therefore, it is justified to assume that most of adult-diagnosed asthma in the current study is also adult-onset asthma. Further, making asthma diagnosis in young children is complex due to lack of appropriate lung function tests and although the incidence of wheezing is substantial, it should not be too eagerly classified as asthma[43]. Furthermore, not every early wheezer develops asthma in adulthood, and neither does every adult-diagnosed asthma patient have wheezing history[7]. Small airway caliber and viral infections can also act as confounders[9]. In conclusion, we believe that adult-onset asthma is a separate entity with unidentified potential for prevention. It should not usually be considered as a reactivation of child-onset asthma, or having similar characteristics.

The response rate in the present study was 52.3%, being moderate, considering that response rates in respiratory epidemiology have declined during the last decades[44,45]. Studies investigating nonresponse bias have found non- and late responders to differ from initial responders by being more often males, younger people and current smokers, correspondingly with the data available in this study[16,44,45]. In addition, these studies report varying results on differences between proportion of asthmatics in responders versus non- and late responders. However, none of these studies stated that using reminders or nonresponse bias significantly affected the prevalence or odds ratios related to asthma, even if the response rate was < 50%. A telephone interview non-responder study was planned as a part of the current study, but ethical permission was not granted. Nevertheless, we conclude that this study might have included some non-responder bias, which mainly affects younger and males.

The main weaknesses of the current study are as follows. Firstly, recall bias is present due to the long recall periods in some asthma cases. Secondly, our responders were more

often older and women and therefore results are susceptible to nonresponse bias. Thirdly, the highest age groups (≥ 70 years) are missing. Finally, due to the inclusion of subjects with significant smoking history, we probably interpreted some COPD as asthma in older subjects. However, the present study also has many strengths. We had a large sample reflecting general population and a relatively good response rate, and used a questionnaire with well proven validity. Subjects were asked about physician-diagnosed asthma which is diagnosed with objective methods and associated to financial benefits in Finland, diminishing recall bias and securing better validity of asthma cases. Lastly, we had a very wide age span which would be extremely difficult to achieve without major drop out prospectively.

In conclusion, adult-onset asthma is a common phenotype and a major burden to the healthcare system. The incidence of adult-onset asthma peaks in middle-aged women. By investigating the poorly understood etiology of new asthma in adult subjects, new approaches to pathogenesis, preventive strategies and effective treatment methods could be discovered. This would lead to upgraded guidelines and major economical and public health improvements.

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