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Epidemiology of Asthma by Age at Diagnosis

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ABSTRACT

Asthma is a heterogenous disease which is suggested to differentiate by age at onset according to previous literature. It seems that adult-onset asthma would have weaker response to asthma medication and worse prognosis than asthma which has occurred in childhood, and that the average patient characteristics would be different between them. However, the previous studies considering age at asthma onset are quite scarce, have rarely been based on population data and have usually left out older adults. In them, asthma is also mostly divided only dichotomously to adult and child-onset asthma, although dividing asthma by more various age at onset groups, like younger and older adults, could also have further importance.

Therefore, the aim of this study was to, in an adult population sample, investigate versatilely age at asthma diagnosis and its association with asthma remission, symptom burden, and other common chronic diseases. The aim was also to investigate age-specific prevalence and incidence of asthma.

This study utilized data which were collected by sending a FinEsS respiratory questionnaire to 16 000 subjects aged 20-69 years during year 2016. The subjects were randomly selected by the Finnish Digital and Population Data Services Agency from Helsinki and Seinäjoki-Vaasa area populations, conforming their age and sex distributions. Asthma was categorized by age at diagnosis in two different ways: firstly, to child (0-17 years) and adult-diagnosed (18-69 years) asthma, and secondly, to early (0-11 years), intermediate (12-39 years), and late-diagnosed (40-69 years) asthma. Age at asthma diagnosis was also used as a continuous variable in the analyses.

The main findings of this study were the following. Totally 8199 (51.5%) subjects responded, 879 (11.1%) reported asthma and 842 additionally reported age at asthma diagnosis. Early-diagnosed asthma was reported by 245 (29.1%), intermediate-diagnosed by 358 (42.5%) and late-diagnosed by 239 (28.4%) subjects.

In the Seinäjoki-Vaasa data (responders N=4173), the 10-year age and gender-specific incidence of new asthma diagnosis was highest in 0-9-year-old males and 40-49-year-old females. Adult-diagnosed asthma (N=271, 63.7%) was the dominant phenotype of asthma in the studied population and became dominant in females by

38 and in males, by 50 years of age as related to child-diagnosed asthma (N=155, 36.3%).

In the whole study data (responders N=8199), late-diagnosed asthma was in remission only in 5% of cases, and as age at asthma diagnosis increased, the probability of being in remission decreased (p<0.001). In early-diagnosed asthma, males were more often in remission than females (36.7% vs. 20.4%, p=0.006). Subjects with adult-diagnosed asthma reported also more asthma symptoms than subjects with child-diagnosed asthma (median 4 vs. 3 symptoms, p<0.001). In multivariable logistic regression analysis including 12 different variables, significant risk factors of attacks of breathlessness in the last 12 months in subjects with physician-diagnosed asthma were female gender, family history of asthma, adult-diagnosed asthma, and allergic rhinitis.

The most common non-respiratory disease in subjects without asthma (18.9%) and with late-diagnosed asthma (42.3%) was hypertension, and in early- (17.5%) and intermediate-diagnosed asthma (21.1%), obesity. Late-diagnosed asthma was significantly more often associated with three or more non-respiratory diseases as opposed to subjects without asthma (p<0.001) or other age at diagnosis groups (p=0.007). The analyses were widely redone by excluding COPD, and it did not affect the significant differences between key variables.

In the light of these results, adult-diagnosed asthma and especially late adult diagnosed asthma is a marked health burden in the general adult population and asthma diagnosed in childhood less common, more prone to be asymptomatic and less associated with multimorbidity. Therefore, both absolutely and relatively speaking, more resources should be allocated to investigation and treatment of adult-diagnosed asthma especially if diagnosed in late adulthood.

TIIVISTELMÄ

Astma on monimuotoinen sairaus, jonka alkamisikä näyttäisi vaikuttavan siihen liittyviin ominaisuuksiin. Niillä potilailla, joilla astma on diagnosoitu aikuisiällä, vaikuttaisi olevan heikompi vaste astman lääkehoidoille sekä huonompi ennuste kuin lapsena astmadiagnoosin saaneilla.

Astman alkamisiän huomioon ottavat tutkimukset ovat kuitenkin harvinaisia, perustuvat harvoin väestötutkimuksiin ja sisältävät usein vain nuorempia potilaita, jättäen vanhemmat ikäryhmät huomiotta. Astman alkamisikä on aiemmissa tutkimuksissa jaoteltu pääosin vain kahteen eri ryhmään, vaikka astman on havaittu eroavan todennäköisesti myös laajemmin erilaisten alkamisiän mukaisten jaotteluiden suhteen.

Tämän tutkimuksen tavoitteena oli tutkia astman diagnoosi-iän yhteyttä astman remissioon, oireiluun ja oiretaakkaan, sekä muihin yleisiin kroonisiin sairauksiin. Lisäksi tavoitteena oli selvittää astman vallitsevuutta ja ilmaantuvuutta eri ikäryhmissä.

Tutkimusmateriaali kerättiin lähettämällä FinEsS hengitystieoireita kartoittava kyselykaavake 16 000:lle 20–69-vuotiaalle tutkittavalle vuoden 2016 aikana. Tutkittavat valittiin satunnaisesti Digi- ja väestötietoviraston tietokannasta Helsingin, Seinäjoen ja Vaasan alueilta väestön ikä- ja sukupuolijakaumaa mukaillen. Astma jaoteltiin diagnoosi-iän mukaan kahdella tavalla: lapsuudessa (0-17-vuotiaana) ja aikuisuudessa (18-69-vuotiaana) diagnosoituun sekä varhain- (0-11-vuotiaana), nuorena aikuisena- (12-39-vuotiaana) ja myöhään (40-69-vuotiaana) diagnosoituun astmaan. Astman diagnoosi-ikää hyödynnettiin myös jatkuvana muuttujana analyyseissa.

Tutkimuksen päätulokset olivat seuraavat. Tutkittavista 8199 (51,5%) palautti kyselykaavakkeen, ja heistä 879 (11.1%) raportoi sairastavansa lääkärin diagnosoimaa astmaa ja 842 raportoi lisäksi iän, jolloin diagnoosi oli asetettu. Astmaa sairastavista 245 (29,1%) raportoi sairastavansa varhain-, 358 (42,5%) nuorena aikuisena- ja 239 (28,4%) myöhään diagnosoitua astmaa.

Kun tarkasteltiin Seinäjoki-Vaasan aineistoa (N=4173), kymmenvuosittainen ikä- ja sukupuoliominainen uuden astmadiagnoosin ilmaantuvuus oli korkein 0-9-vuotiailla pojilla ja 40-49-vuotiailla naisilla. Lisäksi aikuisuudessa diagnosoitu astma

(N=271, 63,7%) oli vallitsevin astman ilmiasu tutkitussa väestössä ja se tuli vallitsevammaksi naisilla 38 ja miehillä 50 vuoden ikään mennessä lapsuudessa diagnosoituun astmaan (N=155, 36,3%) nähden.

Koko tutkimusaineistossa myöhään diagnosoitu astma oli remissiossa vain 5 prosentissa tapauksista, ja astman diagnoosi-iän lisääntyessä remissiossa olevien osuus pienentyi. Varhain diagnosoitua astmaa sairastavat miehet olivat remissiossa useammin kuin naiset (36,7% vs. 20,4%, p<0,006). Aikuisuudessa diagnosoitua astmaa sairastavat raportoivat myös enemmän astman eri oireita kuin lapsuudessa diagnosoidut (mediaani neljä vs. kolme oiretta, p<0,001). Logistisessa monimuuttujamallissa viimeisen 12 kuukauden aikana ilmaantuneen äkillisen hengenahdistusoireen tilastollisesti merkitseviä riskitekijöitä olivat naissukupuoli, astman esiintyminen perheessä, astman diagnoosi aikuisuudessa ja allerginen nuha.

Yleisin ei-hengityselinperäinen sairaus astmaa sairastamattomilla (18,9%) ja myöhään astmadiagnoosin saaneilla (42,3%) oli verenpainetauti. Vastaavasti, lihavuus oli yleisin varhain- (17,5%) ja nuorena aikuisena diagnosoitua astmaa sairastavilla (21,1%). Myöhään diagnosoitu astma liittyi useammin kolmen tai useamman sairauden yhtäaikaiseen esiintyvyyteen verrattuna astmaa sairastamattomiin (p<0,001) tai muihin astmadiagnoosin saaneisiin (p=0,007). Analyysit tehtiin laajalti myös niin, että keuhkoahtaumatauti oli poissuljettu, eikä tämä muuttanut merkitseviä tuloksia oleellisesti.

Tämän tutkimuksen tulosten perusteella aikuisuudessa diagnosoidulla ja etenkin myöhäisessä aikuisuudessa diagnosoidulla astmalla näyttäisi olevan huomattava vaikutus väestön sairaustaakkaan. Toisaalta lapsuudessa diagnosoitu astma näyttäisi olevan vähemmän yleinen, todennäköisemmin remissiossa tai lievempioireinen ja harvemmin yhteydessä monisairastavuuteen. Näiden tulosten perustella, aikuisuudessa, ja erityisesti myöhään aikuisuudessa diagnosoidun astman tutkimukseen, hoitoon ja seurantaan tulisi panostaa aikaisempaa enemmän resursseja sekä absoluuttisesti, että suhteellisesti verrattuna lapsuudessa diagnosoituun astmaan.

CONTENTS

ABBREVIATIONS

ACO	Asthma-COPD overlap
ANOVA	Analysis of variance
BMI	Body mass index
BMRC	British Medical Research Council
CI	Confidence interval
COPD	Chronic obstructive pulmonary disease
FeNO	Fractional exhaled nitric oxide
GERD	Gastro-Esophageal reflux disease
GINA	Global Initiative for Asthma
IL	Interleukin
ILC2	Type 2 innate lymphoid cell
IgE	Immunoglobulin E
Med	Median
mMRC	Modified Medical research council dyspnea scale
OLIN	Obstructive Lung Disease in Northern Sweden
OR	Odds ratio
PEF	Peak expiratory flow
PPI	Proton pump inhibitor
I, II, III, IV	Publications I, II, III, and IV
Q_1-Q_3	Quartiles
SD	Standard deviation
T2	Type 2
Th2	T-helper 2
TIA	Transient ischemic attack
VGDF	Vapors, gases, dusts, and fumes

ORIGINAL PUBLICATIONS

I   Age- and gender-specific incidence of new asthma diagnosis from childhood to late adulthood. Honkamäki J, Hisinger-Mölkänen H, Ilmarinen P, Piirilä P, Tuomisto LE, Andersén H, Huhtala H, Sovijärvi A, Backman H, Lundbäck B, Rönmark E, Lehtimäki L, Kankaanranta H. Respiratory Medicine 2019;154:56-62. doi:10.1016/j.rmed.2019.06.003.

II   Asthma remission by age at diagnosis and gender in a population-based study. Honkamäki J, Piirilä P, Hisinger-Mölkänen H, Tuomisto LE, Andersén H, Huhtala H, Sovijärvi A, Lindqvist A, Backman H, Lundbäck B, Rönmark E, Lehtimäki L, Pallasaho P, Ilmarinen P, Kankaanranta H. The Journal of Allergy and Clinical Immunology: In Practice 2020;9(5):1950-1959.e4. doi:10.1016/j.jaip.2020.12.015.

III   Age at asthma diagnosis is related to prevalence and characteristics of asthma symptoms. Hisinger-Mölkänen H, Honkamäki J, Kankaanranta H, Tuomisto L, Backman H, Andersén H, Lindqvist A, Lehtimäki L, Sovijärvi A, Rönmark E, Pallasaho P, Ilmarinen P, Piirilä P. World Allergy Organization Journal. 2022;16;15(9):100675 doi:10.1016/j.waojou.2022.100675.

IV   Nonrespiratory diseases in adults without and with asthma by age at asthma diagnosis. Honkamäki J, Ilmarinen P, Hisinger-Mölkänen H, Tuomisto LE, Andersén H, Huhtala H, Sovijärvi A, Lindqvist A, Backman H, Nwaru BI, Rönmark E, Lehtimäki L, Pallasaho P, Piirilä P, Kankaanranta H. The Journal of Allergy and Clinical Immunology: In Practice 2023;11(2):555-563.e4. doi:10.1016/j.jaip.2022.10.024.

AUTHOR'S CONTRIBUTION

The author of this thesis was the main author in all the Publications. In Publication III the main authorship was shared with Hanna Hisinger-Mölkänen, having an equal contribution. The author's contribution to the publications is described as follows.

Publication I   The author took part in planning the study analyses and did all the analyses and writing of the article and revised the article contents by the study group propositions. The author also did the submission process of the article.

Publication II   The author took part in planning the study analyses and did all the analyses and writing of the article and revised the article contents by the study group propositions. The author also did the submission process of the article.

Publication III The author took part in planning the study analyses and did most of the analyses and shared equally the contribution of writing and revising the article with Hanna Hisinger-Mölkänen.

Publication IV   The author took part in planning the study analyses and did all the analyses and writing of the article and revised the article contents by the study group propositions. The author also did the submission process of the article.

1   INTRODUCTION

Asthma is a chronic disease characterized by variable bronchial obstruction and airway inflammation. Asthma affects approximately 10% of adults in the Nordic countries[1–3], and its incidence differs by age and gender[1,4–6]. However, population-based results which report asthma incidence trend up until old adulthood and in both sexes are rare[1], although this information would be important for efficient identification of new asthma and possible preventive measures.

It is known for a long time, that asthma is heterogenous by nature, but the importance of it has unraveled more through studies on asthma phenotypes and endotypes during the recent years[7]. In these studies, age at asthma onset has been recognized as one of the key elements associated with important features of the disease and patient characteristics[7,8].

However, the role of age at asthma onset has quite rarely been considered in asthma studies. This is though the literature suggests that those with asthma occurring in adulthood would have faster and more marked loss of lung function, poorer treatment response and overall prognosis[9–14]. In contrast, child-onset asthma is found to have higher remission rate and better responsiveness to traditional asthma medications[12,15–17].

Furthermore, child-onset asthma is more often associated with hereditary factors whereas adult-onset asthma with environmental factors[12,18,19]. The key patient characteristics are also found to be different - child-onset asthma patients have been more often males and have allergic sensitization, whereas patients with adult-onset asthma more often females and non-atopic[12,20,21]. Lastly, the pathogenetic processes seem to be different between them on average[12,22,23].

Not only are child-onset and adult-onset asthma different, but evidence also exists that adult-onset asthma would further differentiate by age at onset using delineation point in approximately 40 years of age[14,24,25]. However, the literature is lacking in studies which would include older patients with asthma and even more scarce are studies which assess patients with asthma occurring later in adulthood as an independent group.

2 REVIEW OF THE LITERATURE

2.1 Definition and pathogenesis of asthma

Asthma is a common chronic pulmonary disease characterized by variable airway obstruction and inflammation. Airway obstruction in asthma is mainly driven by smooth muscle contraction, but also other factors, such as mucosal oedema, mucus plugging and permanent tissue changes, may contribute. Airway inflammation contributes to hyperreactivity and dysfunction of the bronchial smooth muscle, and excretion of excess mucus in the airways. As inflammation is uncontrolled and chronic, it may cause irreversible and permanent damage to the airways, such as thickening of the basal lamina, hypertrophy of smooth muscle layer, epithelial shedding, and vascular regeneration.[26,27]

Asthma pathogenesis includes different and complex, also largely unidentified, inflammatory mechanisms mediated by environmental, genetic, and epigenetic factors[28–30]. Crudely, inflammation is nowadays commonly characterized dichotomously, to T2 (type 2) and non-T2, although this model most probably does not explain the pathogenesis fully[7].

T2-inflammation comprises Th2 (T-helper 2) cell or ILC2 (type 2 innate lymphoid cell) mediated immune response encompassing interleukins 4, 5, 9, and 13 which recruit eosinophils, and B cells producing IgE (immunoglobulin E)[31]. T2-mediated pathway is described to associate with approximately 50% of asthma and its Th2 response is especially associated with child-onset asthma and hereditary factors, whereas ILC2 with later adult-onset asthma and presumably environmental factors[7,30,32,33]. Non-T2 inflammation is much less understood, but incorporates interleukins 6 and 1β, and neutrophilic inflammation[33].

Cellular profiles of the inflammatory response are variable and can be generally characterized as eosinophilic, neutrophilic, or mixed[26,34]. However, asthma may also be paucigranulocytic, therefore, sparse in granulocytes, and sometimes associated with systemic inflammation markers[32,35]. Nevertheless, comprehensive knowledge of asthma pathogenesis has not been established by date[32], especially regarding adult-onset asthma[36].

2.2   Diagnosis of asthma

2.2.1   Methods and strategies of diagnosis

Diagnostic strategies for asthma depend somewhat on patient age and national practices, and there is not one unambiguous practice agreed on to asthma diagnostics[27]. In this chapter, the diagnostic practices are described following the Finnish practices, which comply GINA (Global Initiative for Asthma) recommendations.

In both children over 3 years of age, and adults, diagnosis is set based on typical asthma symptoms and obligatory objective proof of variable airway obstruction[37,38]. Obstruction is sometimes provocable by certain irritants, such as dry air, physical exertion or experimentally by inhaled methacholine. In addition, asthma therapy trial is a usable diagnostic method. What is important, is that the diagnosis is not based solely on asthma symptoms[26,27].

Furthermore, in children under 3 years of age, objective lung function measures are not available and asthma diagnosis is therefore based on having had a minimum of 2 wheezing episodes per year and fulfilling either at least one of the main criteria (sensitization to respiratory allergens, atopy, or at least one parent having physician-diagnosed asthma), or two side criteria (heightened eosinophils in blood sample, having wheezy episodes without viral infections, or IgE-mediated sensitization to food allergens)[39].

In children approximately 3-6 years of age, who still mostly have too low co-operation to carry out spirometry or PEF (peak expiratory flow) monitoring, the golden standard method to confirm asthma diagnosis in Finland is impulse oscillometry[39]. In older children, mostly similar diagnostic methods are followed as in adults[26,39,40].

In adults in Finland, asthma diagnosis is set most often based on PEF monitoring of two weeks, or spirometry. Other diagnostic strategies include methacholine challenge test, exercise challenge test, or asthma treatment test[2637].

The diagnosis can be set in the primary healthcare in most of the asthma cases, but especially in children, secondary healthcare is also utilized often in diagnosis-making and is preferred in children 0-6 years of age. In other age groups, secondary healthcare is utilized in the diagnosis-making if asthma is difficult to diagnose.[26,39]

2.2.2 Difficulties in diagnosis and misdiagnosis of asthma

Asthma is known to be difficult to diagnose in many cases. This is most probably due to variation between symptomatic and non-symptomatic periods, and markedly apparent in areas in which availability of methods to prove variable airway obstruction is poorer. There can also be cultural differences in reporting symptoms to a physician[41]. In older adults, possible difficulties in identifying and communicating the symptoms further complicate the diagnosis-making process[23].

In Finland, as described in the previous chapter, asthma diagnosis in adults and older children is confirmed by objective lung function testing, and this is also a criterion for receiving governmental asthma medication reimbursement[1]. However, even the standard diagnostic methods have their difficulties. The diagnostic protocols in children, suggested by multinational consortiums, are quite insensitive or difficult to implement in the clinical practice[42]. Sensitivity of current primary lung function tests for identifying asthma are neither fully satisfactory – sensitivity even as low as <30% in spirometry[43], and <50% in PEF monitoring in asthma diagnosis-making have been reported[38]. This leads to a risk of marked rates of false negative cases in asthma. However, PEF monitoring also predisposes to false positive asthma diagnoses since its results are reported by the patient itself.

In addition, if asthma is not aimed to be diagnosed based on objective measures, making false positive diagnoses is also an important issue. There are reports from Canada and The United Kingdom, that over 30% of asthma cases may be misdiagnoses[41,44–47]. Reports suggest that objective lung function testing is not always applied in the diagnosis-making in certain areas, such as Canada and Britain, though necessary[48,49].

2.2.3 Self-reported age at asthma diagnosis

Self-reported asthma is most often assessed by asking age at asthma onset from study subjects in previous studies. This method has been estimated notably trustworthy in three separate studies in which the recall period was approximately 5-10 years[50–52]. However, asthma age at onset is difficult to define since asthma symptoms may occur years before diagnosis, and therefore, age at asthma diagnosis would a more precise parameter and easier to integrate with the clinical context.

In Finnish data, sensitivity, and specificity of self-reported asthma diagnosis to classify previously diagnosed asthma has been very good[53]. However, studies assessing asthma age at diagnosis and its validity in self-reported assessment are much less common than in age at asthma onset.

2.3 Treatment of asthma

The most common medicinal treatments of asthma are similar in all age groups. The cornerstone of asthma treatment is regular inhaled corticosteroids, which alleviate airway inflammation. These are often combined with short-acting inhaled beta-2-agonists which inflict bronchodilation effect, administered if necessary. Regular long-acting inhaled beta-2-agonists and anticholinergics may be added to treatment.

Other treatment methods include oral leukotriene antagonists, such as montelukast, which is most often combined with inhaled medications. More novel treatment possibilities for severe asthma, which are increasingly available to more patients, are biologic medications, at the time mostly anti-IL-5, anti-IL-4/13, and anti-IgE antibodies. Oral corticosteroids are used as rescue medication during acute exacerbations, but maintenance use should be avoided[26,27].

Allergic conditions, chronic rhinitis and sinusitis also coexist quite often with asthma and treating these diseases effectively also benefits asthma control[26,27]. In addition, non-medicinal important treatment methods of asthma include weight control, regular exercise, and cessation of cigarette smoking[26].

2.4 Epidemiology of asthma

2.4.1 Prevalence

The estimated adult ever asthma prevalence is approximately 10 percent in recent Nordic studies[54,55]. Due to differences in accessibility to the healthcare, diagnostic tools, and practices, as well as true differences in asthma occurrence rate, the prevalence varies markedly by the studied area[56–58].

Prevalence of asthma has risen many decades in the Nordics and other parts of the Europe, but reportedly it has stabilized at the population level[59]. The most

marked reasons for the increase are supposedly related to the hygiene hypothesis, enhancement of asthma identification, and better diagnostic strategies[60].

Asthma prevalence is different by age, and it can be handled at least in two importantly different ways – ever having had asthma or currently active asthma prevalence, due to remission potential in asthma. As well as time, area, and age, sex is an important modifier of asthma prevalence[1,3,61].

Prevalence of asthma by age at onset

A quite recent Australian study reported child-onset asthma prevalence of 7.7% and adult-onset of 7.8% (delineation point at 13 years of age) from a population cohort with subjects up to 44 years of age[62]. Further, in a US large scale telephone survey including subjects ≥18 years of age, proportion of adult-onset asthma was 57% and child-onset 43%, with delineation point in 18 years of age. In this study, child-onset asthma was reported by 56% of males and 36% of females with asthma[61]. Lastly, a US prospective population cohort with subjects up to 55 years of age found that 47% of subjects with asthma had child-onset disease (<18 years) and adult-onset asthma became the dominant phenotype in women already at age 40 years[63].

2.4.2 Incidence

Incidence of asthma varies by age. It has been shown to be high in young children, especially males[1,4]. However, diagnostics is particularly difficult in very small children, and misdiagnosis most probably contributes to the high remission rate in asthma diagnosed in early age[15,16,45,64,65]. The incidence seems to rise again in adolescence, during puberty, and then rise again after young adulthood[1,4]. Studies reporting incidence in older age (>60 years of age) are scarce, but in one study, the incidence seemed to increase even more sharply towards elderly age[1]. Asthma incidence studies in >70-year-old adults are very rare.

A study from Canada estimated so-called lifetime asthma incidence to be approximately 4/1000/year[66] up until 79 years of age, and another from Italy 2,6/1000/year[4] up until 44 years of age. In Finnish data, incidence of asthma medication reimbursements was 2.5/1000/year[1].

Incidence of asthma by age at onset

Regarding asthma age at onset specific incidence, in the first 9 years of life, incidence of physician-diagnosed asthma of 16/1000/year has been reported[67]. In another study from the Netherlands, incidence of physician-diagnosed asthma validated by medical records, was reported to be 6,7/1000/year in children up to 18 years of age[5]. These are much lower estimates than incidence of wheezing which has been estimated to be in between 23-53/1000/year during the first 6-9 years of life[64,67,68]. It is evident that the asthma incidence in children varies markedly by diagnosis criteria, which are not standardized between countries.

For adult-onset asthma, from multiple studies pooled together, incidence estimates of 4,6/1000/year in females and 3,6/1000/year in males are reported[69]. The pooled studies included subjects with age at asthma onset at 15-70 years of age, and the most often used delineation point for child and adult-onset asthma was 12 years of age. Similar or little lower incidence estimates have been reported from Nordic studies regarding adult-onset asthma[70–72]. Very age-specific incidence estimates for asthma have very rarely been described in subjects over 50 years of age.
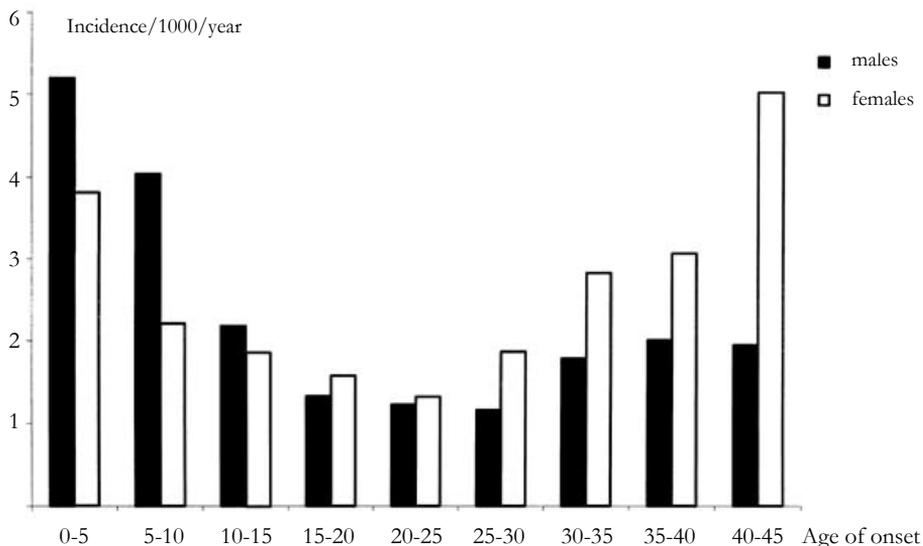
Figure 1. Adjusted age and gender-specific incidence of asthma per 1000 persons per year in Italy. Modified from de Marco et al. J All Clin Immunol 2002.

2.4.3   Risk of asthma

The risk of asthma varies by age, like the age trend of asthma incidence indicates. However, there are several other risk factors which seemingly predispose to occurrence of asthma. These factors can be roughly separated to two categories: environmental and hereditary factors, although they somewhat overlap[12]. In addition, epigenetics, the interplay between environmental factors and genetics, is also most presumably an important, mostly undiscovered factor which modifies asthma risk[73–75].

Generally, hereditary risk factors of asthma play a more important role in child-onset, whereas environmental factors in adult-onset asthma[12].

The most important hereditary factors which increase asthma risk in childhood are atopy, male sex, lower lung function, and family history of asthma[76–80]. Sex hormones and allergic sensitization also play a role in adult-onset asthma, and sex affects asthma risk differently by different age periods in adulthood[81–84]. [18,19]

The most important environmental risk factors identified in adult-onset asthma are smoking, high BMI, and exposure to gases, dusts or fumes[20,36,62,85–87]. Most of them can not affect children straightforwardly since the exposure needs to be sufficient. However, asthma in childhood is found to be associated with viral infections, microbiome, and exposure to tobacco smoke or air pollution[88–91].

Epigenetics is under a marked interest in the scientific context. Epigenetics refers to stable and heritable changes in cell function that are not evident in the DNA sequence. However, little is still known how marked proportion of asthma risk is associated with epigenetics[74,75]. Asthma runs in families, but from genome-wide studies, quite little relevance regarding asthma occurrence have been found[92]. Therefore, epigenetics could be the key to understanding much more of the individual risk of asthma[74,75,93].

2.5   Asthma symptoms

The most typical asthma symptoms are variable breathlessness, cough, dyspnea, and wheezing. The symptoms are variable over time, and sometimes prone to worsening due to certain irritants.[26,27]

In children, the most common asthma symptoms have been found to be wheezing and waking up for coughing[94], whereas in adult population, shortness of

breath and wheezing[54]. Nevertheless, variability occurs in reported asthma symptoms between subjects[46,87]. A population study including subjects aged 16-75 years estimated multi-symptom asthma (three or more symptoms) prevalence to be 2%, and more common in women[95]. In a Chinese population study, all the studied asthma symptoms increased in the population by age[96].

It is inconclusive, if asthma symptom burden and lung function or airway inflammation are associative[95,97]. It must also be considered that not any respiratory symptom is specific to asthma and many symptoms may overlap with other diseases[98].

There are few previous studies which have compared asthma symptom burden between child and adult-onset asthma, and they have found very little differences between them[20,62,99].

2.6   Remission of asthma

2.6.1   Concept and definition of asthma remission

Asthma is known to have a tendency to remit. Asthma remission has nowadays considered to have generally two specifications, on treatment and off treatment remission[100], but in this study, off treatment remission was assessed.

Asthma remission is mostly and traditionally defined in the previous literature as a period preceded by a year of symptomless time without a need for asthma medication, however, it is generally considered that complete remission would also require that the inflammatory biomarkers in asthma would be at least minimal[101]. As remission occurs, the time how long the remission will last may be difficult to estimate, and asthma may alternate between remitted and currently active state with various periods[102].

2.6.2   Asthma remission by age at diagnosis

Asthma remission by age at asthma onset has mostly been studied in samples which study either child-onset or adult-onset asthma, not both, which makes the comparison difficult.

In children, depending vastly on the study sample, remission may be estimated as high as 75% by young adulthood[15]. In studies where diagnosis is based on objective lung function test and not solely on symptoms, remission rate is estimated to be 20-30% in early school-aged children up until young adulthood[1,103].

In adults, asthma remission has been studied in both prospective and cross-sectional study settings. Adult-onset asthma is estimated to remit in only 3-17%, mostly under 10%, of cases when approximately 2-12 years had passed from the initial diagnosis in prospective cohorts[9,10,70,71,104–108]. In one of these studies, also a subanalysis was made in different adult-onset asthma groups[106]. The remission rates in that study for different asthma onset ages were 9% for 0-19 years, 6% for 20-39 years, and 4% for ≥40 years of age at onset. Some of the studies included also older adults up to >75 years of age.

2.6.3   Risk factors for current asthma or non-remission

Current asthma can be defined as asthma which is currently symptomatic or in need of medication to stay asymptomatic. Also, it could be interpreted as asthma which has fulfilled these criteria during the previous year, which is usually set as a delineation point between current and remitted asthma[101].

The risk factors for current and persistent asthma compared to remission in childhood are most often reported to be lower lung function or more difficult asthma, allergic sensitization, family history of asthma, and female sex[17,103,109,110].

In adult-onset asthma, non-remission in asthma or uncontrolled disease has been associated with higher blood neutrophils, higher BMI, smoking, and rhinitis or nasal polyposis[10,104,108].

2.7   Age at asthma onset

Asthma is considered to consist of marked heterogeneity. However, age at asthma onset seems to associate with different fundamental characteristics of asthma and is a consistent and quite easily identifiable patient characteristic. Particularly, these include asthma pathogenesis and inflammation profile, tendency to remit, responsiveness to treatment, and patient characteristics. Commonly found

differences between age at asthma onset defined phenotypes are illustrated in Table 1.[9,12,20,111]

As child-onset asthma is traditionally a well identified subcategory of asthma, doubts that adult-onset asthma would be a separate entity in asthma, exist[12,112]. This is mostly due to evidence, that child-onset asthma has a high remission rate, but it would also have a considerable rate of relapse at least in young adulthood[64,68]. In addition, there are reports that lung function deficits present in mid-adulthood would mostly have been present already in childhood[112,113].

However, there is good evidence that not every adult-onset asthmatic has had wheezing symptoms in childhood[64,114], and certain fundamental parameters are different in child- and adult-onset asthmatics[12,21,111], which are arguments that quite strongly disagree with the allegations that these subtypes of the disease would be united.

Table 1. Common features of patients with adult or child-onset asthma. Modified from Dunn et al. Allergy 2018.

	Adult-onset asthma	Child-onset asthma
Age of onset	Variable but typically as an adult	Age <12
FEV1	Higher	Lower
Severity	Variable	Variable
TH2-mediated	Variable	(+)
Atopy	(−)	(+)
Family history	(−)	(+)
Obesity	(+)	(−)
Tobacco use	(+)	(−)

2.8   Phenotypes and endotypes of asthma

2.8.1   Phenotypes of asthma

Asthma phenotypes have been an important study field in asthma during the 21st century. Phenotypes are clusters of asthma patients which hold similar characteristics between each other. One of the main premises of studying phenotypes has been that phenotypes would match the underlying pathogenesis and therefore accelerate deployment of more personalized asthma treatment and helping to unravel yet unidentified pathogenetic mechanisms[7]. Though, this has not been the case entirely since one phenotype may include several different pathogenetic mechanisms[7,111].

Different phenotyping studies have used different parameters to define phenotypes, mostly utilizing cluster analyses[7,115,116]. Not often have the phenotypes been analogous between the studies. However, certain traits have been clustered together in many separate studies and some phenotypes have been recurrent[36]. These include child-onset allergic asthma, adult-onset non-allergic eosinophilic asthma and adult-onset non-allergic and non-eosinophilic asthma[8]. Figure 2 illustrates some of the commonly described phenotypes. As may be interpreted from the abovementioned consistently identified phenotypes, the most important parameters which delineate phenotypes seem to be allergic sensitization and eosinophilic status, as well as age at asthma onset[8].
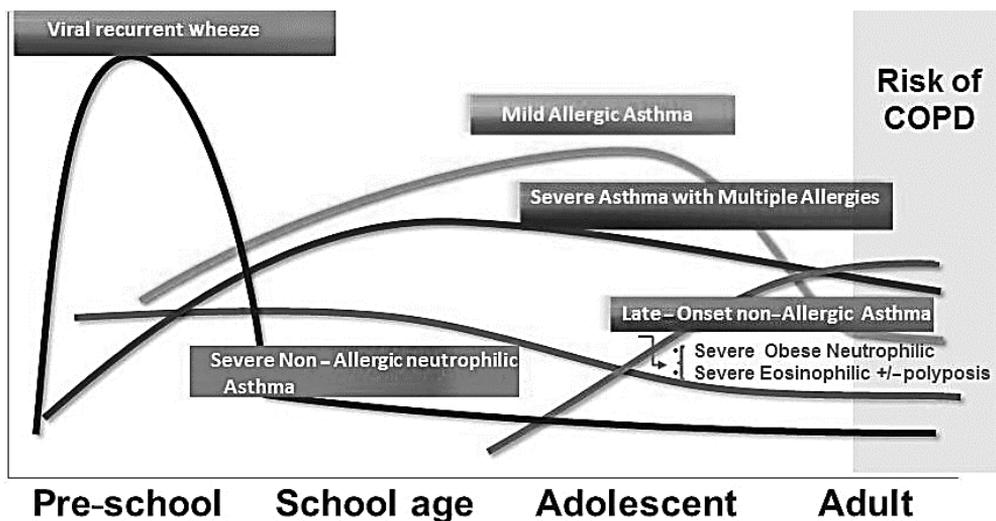
Figure 2. One way to illustrate certain asthma phenotypes. Adult-onset asthma is taken into account only in a quite narrow manner, which is not unusual currently in the field of asthma research. Modified from Just et al. Clin Exp All 2017.

2.8.2 Endotypes of asthma

Asthma endotypes, apart from phenotypes, emphasize the pathogenetic molecular mechanisms in asthma categorization[31,117]. By understanding endotypes the right treatments could be guided to the right patients. However, endotypes are quite difficult to study, since in most cases tissue samples and multiple clinical tests would be needed to investigate them[118], and moreover, the mechanisms of asthma inflammation are not yet comprehensively understood[31].

There is already some knowledge of the possible endotypes[117], and of the found endotypes, the most consistent is the type-2 inflammatory endotype[119–121]. Otherwise, many preliminary endotypes of asthma have been proposed, some examples being allergic fungal adult asthma, and child-onset asthma low in sphingolipids[117,122–124].

2.9 Asthma, comorbidities, and multimorbidity

2.9.1 Asthma and multimorbidity

Multimorbidity is mostly an understudied, however an important and growing field of research. Comorbid diseases in patients with asthma have previously been scarcely taken into account as important factors in asthma prognosis, or confounders[125], although only quite recent evidence suggests that multimorbidity is a major cause of asthma-related health and financial burden[126–129].

2.9.2 Asthma and respiratory comorbidities

Asthma, and especially childhood asthma, is well known to coexist very often with allergic sensitization[130,131][132], and allergic conditions are also included in the clinical practice predicting the risk of asthma in young children[39]. Asthma, chronic rhinosinusitis, nasal polyposis, and COPD do also quite commonly coexist in adults[132,133]. In a very recent prospective study, early-onset asthma was associated with higher risk of COPD than adult-onset asthma[134], though another study examining difficult asthma reported the opposite association[135]. There is also evidence of association of bronchiectasis and dysfunctional breathing with asthma[132].

2.9.3 Asthma and non-respiratory comorbidities

Subjects with asthma have been found to have more other common chronic diseases than subjects without asthma[136–138]. These include dyspepsia[136,139], cardiovascular diseases[140–142], obesity[138,143], mental disorders[136,138,144,145], osteoporosis[136], diabetes[136], autoimmune thyroid disease[146], and sleep apnea[147]. There are estimates that over 50% of adults with asthma would have also at least one non-respiratory comorbid condition[127,148].

Age at asthma onset and non-respiratory comorbidities

Comorbidities have been investigated often age-wise, but very rarely by taking age at asthma onset into account. What we previously know about the associations between child and adult-onset asthma and chronic diseases, is that adult-onset asthma seemingly associates with cardiovascular diseases[140] and metabolic syndrome[149], but the few studies have not found that child-onset asthma would associate with any studied non-respiratory disease[142,149,150]. There is no previous evidence from comparing subjects without asthma and subjects with asthma categorized by age at onset, or to compare adult-onset asthma by age at onset, to the best of our knowledge.

3 AIMS OF THE STUDY

We hypothesized that adult-diagnosed asthma would be more prevalent, less well controlled and associate with more comorbid diseases than child-diagnosed asthma, as studied in an adult general population. Also, we hypothesized that older age at diagnosis of asthma would associate with less controlled asthma.

The first study aimed to investigate prevalence and incidence of asthma, specific to age and gender. It also aimed to report if child or adult-diagnosed asthma is more common in the adult population, and which of them is dominant in certain age groups.

The second study's study questions were, how much of asthma would be in remission during the time of the study, and how age at asthma diagnosis and gender affected this proportion. Risk factors of currently active asthma were also assessed.

The aim of the third study was to study the hypothesis, that adults with asthma diagnosed in adulthood have more asthma symptoms than those adults with child-diagnosed asthma, and that the symptoms would differ between asthma diagnosed at childhood or adulthood.

The fourth study assessed how age at asthma diagnosis affected the number and quality of chronic diseases coexistent with asthma and compared adults without and with asthma by age at asthma diagnosis. The study also assessed the odds ratio of different chronic conditions in patients with asthma diagnosed at different ages as opposed to subjects without asthma.

4   MATERIALS AND METHODS

4.1   The FinEsS study

This study was a part of the FinEsS (Finland, Estonia, Sweden) study. The FinEsS study is a multicentre questionnaire study which was initiated in 1996 in Sweden[151]. Samples from different centres have been collected in years 1996, 2006 and 2016.

4.2   Study planning and data acquisition

This study data were collected starting in February 2016 from Helsinki and Western Finland (Seinäjoki and Vaasa) areas. A population sample of 8,000 subjects from both areas, totally 16,000 20-69-year-old adults was collected by the Finnish Digital and Population Data Services Agency conforming the age and gender distributions in the areas. The study subjects were sent a FinEsS respiratory questionnaire, and up to three postal rounds were utilized in case of nonresponse.

Power calculations was estimated before sample collection to define sufficient sample size considering the study questions, taking potential non-response into account.

The study was approved by the Ethics Committee of the Helsinki University Hospital. Permission to implementation of a non-responder telephone survey was applied for but not granted.

4.3   The FinEsS questionnaire

The FinEsS questionnaire is modified from the Obstructive Lung Disease in Northern Sweden (OLIN) questionnaire, which is also modified from the Swedish version of the British Medical Research Council (BMRC) questionnaire[152]. It contains questions on basic information of the subjects as well as questions

concentrated on respiratory health, allergies, lifestyle, family history, and different chronic diseases. The Finnish version of the questionnaire is available online[I].

4.4   Definitions of key parameters

Most of the study parameters were based on the responses to the FinEsS questionnaire questions, which can be found online[59,I]. Otherwise, information on age and sex of the invited subjects were received from the Finnish Digital and Population Data Services Agency.

The key parameters were defined as follows:

physician-diagnosed asthma by a positive response to "Have you been diagnosed by a doctor as having asthma?"

age at asthma diagnosis "What age were you when asthma was diagnosed?"

child-diagnosed asthma as asthma was diagnosed at 0-17 years of age and *adult-diagnosed asthma* as 18-69 years.

early-diagnosed asthma as asthma was diagnosed at 0-11 years of age, *intermediate-diagnosed asthma* as 12-39 years and *late-diagnosed asthma* as 40-69 years.

current asthma as reporting *physician-diagnosed asthma* and giving a positive answer to at least one of the following questions: "Have you had shortness of breath during the last 12 months", "Have you had any wheeze during the last 12 months", or "Do you currently use asthma medication"?

remitted asthma as reporting *physician-diagnosed asthma* but not fulfilling the criterion for *current asthma*.

number of non-respiratory diseases comprised of the following 14 diseases: hypertension, arrythmia, heart failure, coronary artery disease, stroke or TIA, depression, anxiety or panic disorder, diabetes, GERD, chronic kidney failure, sleep apnea, osteoporosis, painful condition, and obesity. The diseases were asked in the questionnaire systematically with response options yes or no.

4.5 Statistical methods

4.5.1 General statistical methods

The statistical analyses were conducted with SPSS Statistics (IBM, USA). All the analyses in final publications were revised by a MSc in biostatistics.

Basic statistical methods were utilized as needed. Chi-Square test was used to statistically compare two or three categorical groups, and when the sample size was small and two categorical groups were compared, alternatively Fisher's exact test.

For comparison of two continuous variables, Mann-Whitney test was utilized if the samples were non-normally distributed. Whereas, when it was normally distributed, t-test was used. If three continuous variables were compared, in non-normally distributed and normally distributed variables, Kruskal-Wallis test and one-way ANOVA were utilized, respectively. Normality of continuous variable distributions was assessed both visually and with Kolmogorov-Smirnov test.

Binary logistic regression and linear regression analysis were used in both univariate and multiple forms to do statistical testing, specify effect sizes, and control confounding. In multiple analysis, the covariates were chosen to the analyses primarily by weighing clinical relevance.

In all studies, 95 percent confidence interval was utilized and p-values <0.05 were considered statistically significant.

4.5.2 Method for incidence calculation

Population at risk for asthma incidence for each age in years was calculated year by year in Publication I (I) and in 5-year groups for the thesis with the following method. We took the number of responders as the base number for calculations, and subtracted firstly, number of subjects which reported asthma diagnosis before the age point for which the population at risk was calculated, and secondly, subjects which were younger than that age point. Incidence was calculated by dividing the incident asthma diagnoses by population at risk year by year and calculating means from these numbers as necessary for the specific analyses. Subjects which reported physician-diagnosed asthma but not age at asthma diagnosis were excluded from this specific analysis.

4.5.3   Sensitivity analyses

Sensitivity analyses were made to support the results and analyses were made in clinically relevant subpopulations. Separate analyses in which COPD was excluded were made for the main results in Publications II, III and IV (II, III, IV). Analyses excluding the youngest age groups were also made separately, additionally to age stratification in IV.

To unify data collected from different centres, subjects lacking responses to questions about smoking habits were excluded from the analyses.

5   SUMMARY OF THE RESULTS

5.1   Sample formation (II)

Figure 3 illustrates, how the path from the initial sample to the analysed population was conformed in both study centres, Helsinki and Seinäjoki-Vaasa.
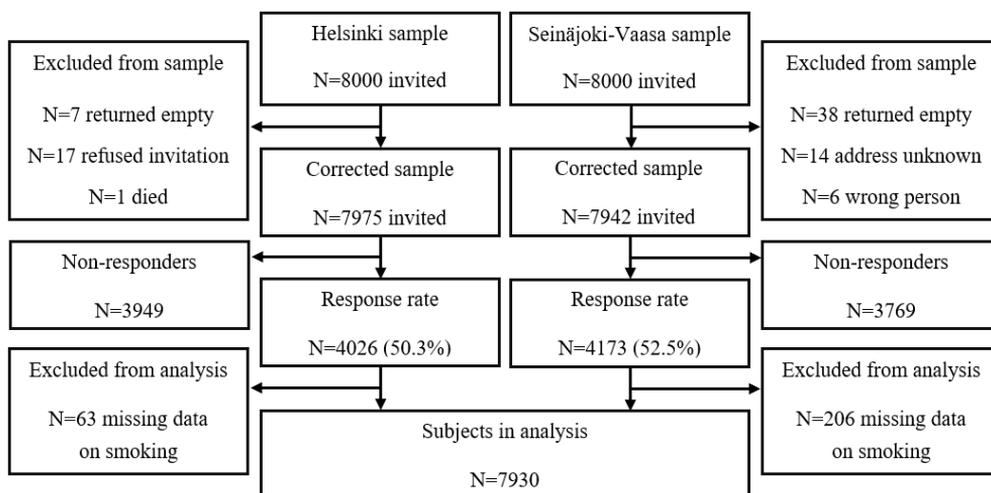
Figure 3.   Flow chart of data management.

5.2   Description of the study subjects and non-responders (I, III)

After three consecutive postal rounds, totally 8199 (51.5% of the corrected sample) of the invited subjects responded to the questionnaire. Median age of the responders was 50 years, and 44.9% of responders were males, whereas median age of the non-responders was 36 years in Helsinki and 40 years in Western Finland, and non-responders were more often males (53.1%). Responders with incomplete responses on smoking habits were excluded (N=269) to uniform study data between centres.

Table 2.   Basic characteristics of study subjects in Helsinki and Seinäjoki-Vaasa combined data.

	Responders N=7942	
	Median	**IQR**
Age	49	35-61
	Mean	**SD**
BMI	26.1	6.3
	N	**%**
Female	4353	54.9
Allergic rhinitis	1783	22.5
Smoking		
Current	1716	21.6
Ex	1967	24.8
Never	4247	53.6
Family history of asthma	1915	24.1
COPD	178	2.2

5.3 Basic epidemiology of asthma by age at diagnosis in the Seinäjoki-Vaasa sample

5.3.1 Seinäjoki-Vaasa sample basic study descriptions (I)

In the Seinäjoki-Vaasa sample, of the invited 8000 subjects, 4173 (52.3% of the corrected sample) responded. The responders were more often females (55.5% vs. 47.4%) and older (median age 53 vs. 40 years) as compared to the non-responders. Subjects with incomplete smoking data were excluded (N=206) from further analyses.

Table 3.   Basic characteristics of responders in the Seinäjoki-Vaasa study sample.

	Responders N=3967	
	Median	**IQR**
Age	53	38-63
	Mean	**SD**
BMI	26.7	4.9
	N	**%**
Female	2069	52.2
Allergic rhinitis	706	17.8
Smoking		
Current	798	20.1
Ex	1086	27.4
Never	2083	52.5
Family history of asthma	1010	25.5
COPD	99	2.5

5.3.2   Prevalence of asthma (I)

Physician-diagnosed asthma was reported by 445 (11.2%) and additionally, age at asthma diagnosis by 427 subjects. Median age at asthma diagnosis was 21 (IQR 7-43) years. Proportion of child-diagnosed asthma was 36.3%, and adult-diagnosed asthma 63.7% of all physician-diagnosed asthma (Figure 4). The child-diagnosed asthma proportions were 41.6% in males and 32.2% in females (p=0.046).
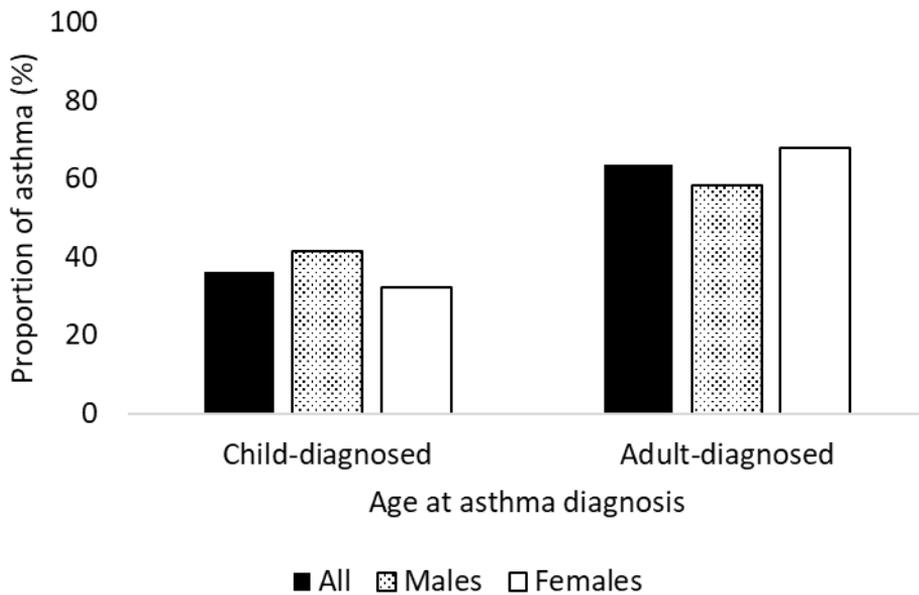
Figure 4. Proportion of child and adult-diagnosed asthma in all subjects, males and females with physician-diagnosed asthma.

To assess prevalence and incidence of asthma at different aged subjects, we categorized subjects to 5-year age groups. Prevalence of child-diagnosed asthma was highest in 20-24-year-old subjects, and adult-diagnosed asthma in 65-69-year-old

subjects of the 5-year categories (Figure 5). In subjects ≥45 years of age, 55.2% had asthma diagnosed after 40 years of age (late-diagnosed asthma).
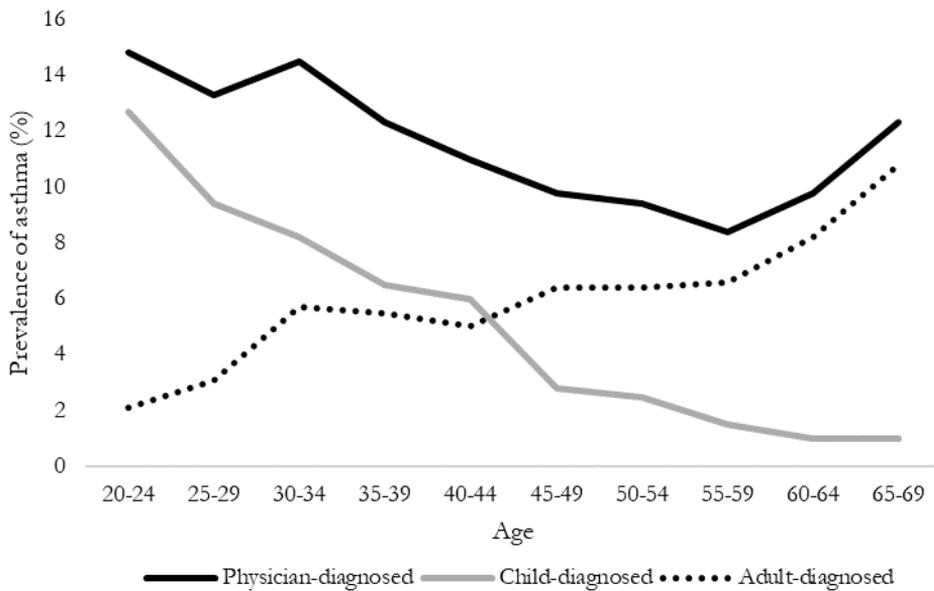
Figure 5. Prevalence of physician-diagnosed asthma, child-diagnosed and adult-diagnosed asthma in 5-year age categories. Regarding child-diagnosed asthma, cohort effect is evident.

Adult-diagnosed asthma became the dominant phenotype in females by 38 and in males, 50 years of age as related to child-diagnosed asthma.

5.3.3   Incidence of asthma (I)

Subjects who reported physician-diagnosed asthma but not age at asthma diagnosis were excluded (N=18). Incidence of asthma during ages 0-69 years for the whole study population was 2,2/1000/years (Table 4). Incidence in 5-year age groups was highest in all subjects in 55-59 years of age, in males in 5-9 years of age and in females in 40-44 years of age (Figure 6).

Table 4. Incidence of physician-diagnosed, child-diagnosed and adult-diagnosed asthma per 1000 persons per year in all subjects, males, and females.

Asthma incidence/1000/year	All	Males	Females
Physician-diagnosed (0-69 years)	2.2	2.0	2.4
Child-diagnosed (0-17 years)	2.2	2.3	2.1
Adult-diagnosed (18-69 years)	2.2	1.8	2.6
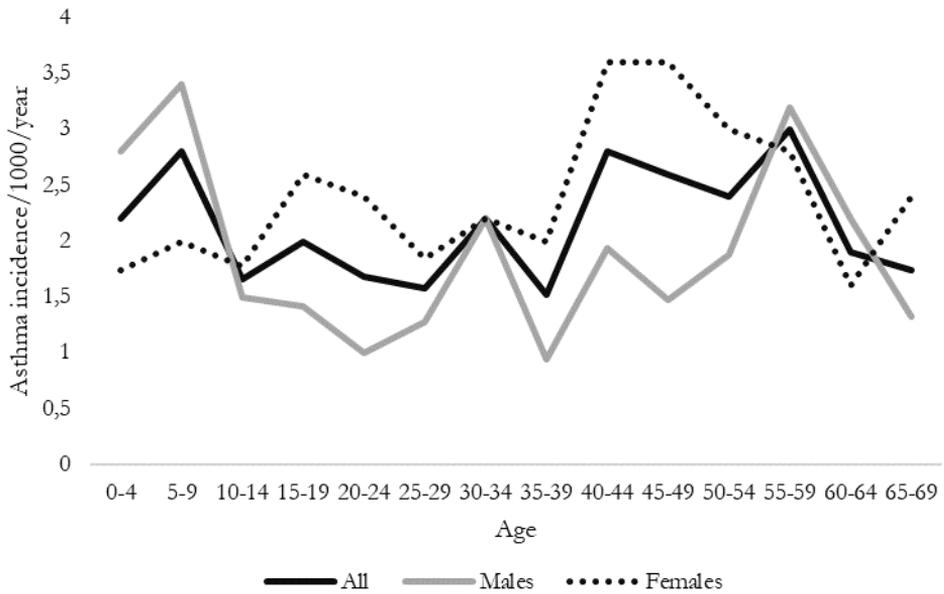
Figure 6. Incidence of asthma in all subjects, males, and females in 5-year age groups.

5.4   Asthma symptoms and current asthma (II, III)

The rest of the results are analyzed from the combined Seinäjoki-Vaasa and Helsinki study sample (N=8199). Totally, 82.2% (N=692) of subjects with physician-diagnosed asthma had current asthma by definition. Of subjects with child-diagnosed asthma, 72.0% (N=247) and with adult-diagnosed asthma, 89.2% (N=445) had current asthma (p<0.001). Currently (≤12 months) asthma medication was used by 616 (73.2%) subjects with physician-diagnosed, 148 (60.4%) with child-diagnosed and 468 (78.4%) with adult-diagnosed asthma (p<0.001).

Attacks of breathlessness was the most common asthma symptom in all subjects with asthma, and in child and adult-diagnosed asthma categories. All the analyzed asthma symptoms were significantly more prevalent in subjects with adult-diagnosed than child-diagnosed asthma (Table 5).

Table 5. Prevalence of different asthma symptoms in subjects with physician-diagnosed, child-diagnosed, and adult-diagnosed asthma, and statistical comparison of the latter two, adjusted by age. Dyspnea mMRC≥2 indicates slow walking due to dyspnea.

	Physician-diagnosed asthma N=842		Child-diagnosed asthma N=343		Adult-diagnosed asthma N=499		
	N	%	N	%	N	%	P
Wheeze	452	53.7	158	46.1	294	58.9	**<0.001**
Longstanding cough	297	35.3	88	25.7	209	41.9	**<0.001**
Sputum production	257	30.5	75	21.9	182	36.5	**0.006**
Asthmatic wheeze	489	58.1	82	23.9	145	29.1	**0.034**
Dyspnea in cold	437	51.9	152	44.3	285	57.1	**0.002**
Dyspnea in exercise	444	52.7	162	47.2	282	56.5	**0.046**
Dyspnea mMRC≥2	228	27.1	52	15.2	176	35.3	**0.007**
Morning dyspnea	342	40.6	119	34.7	223	44.7	**0.001**
Attacks of breathlessness	552	65.6	183	53.4	369	73.9	**<0.001**

As the number of different asthma symptoms were analysed between child and adult-diagnosed asthma, subjects with adult-diagnosed asthma had five or more symptoms more often than subjects with child-diagnosed asthma in age-adjusted analyses (Figure 7). Overall, subjects with adult-diagnosed asthma reported more asthma symptoms than subjects with child-diagnosed asthma (median 4 vs. 3 symptoms, $p<0.001$).
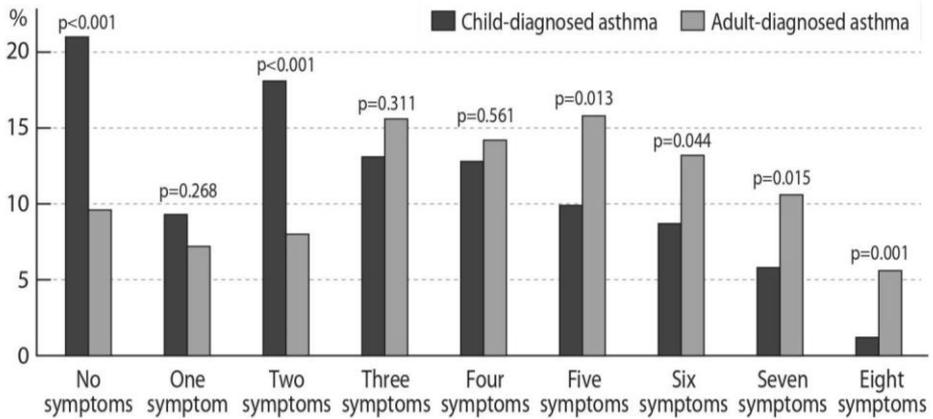
Figure 7. Number of different asthma symptoms in subjects with physician-diagnosed asthma by age at asthma diagnosis and statistical comparison between child and adult-diagnosed asthma, adjusted by age.

A binary multivariable regression analysis was conducted to find significant risk factors of attacks of breathlessness in the last 12 months in subjects with physician-diagnosed asthma. The covariates were gender, family history of asthma, smoking, occupational exposure to VGDF, living in rural area in childhood, living on a farm in childhood, BMI, age at asthma diagnosis, exercise per week, allergic rhinitis, age, and COPD (Table 6). The significant risk factors with highest effect size for attacks of breathlessness in the last 12 months were adult-diagnosed asthma in physician-diagnosed asthma (OR=2.41, 95% CI 1.64-3.54, p<0.001), allergic rhinitis in child-diagnosed asthma (2.25, 1.33-3.79, p=0.002), and COPD in adult-diagnosed asthma (2.37, 1.05-5.35, p=0.038).

Table 6. Risk factors of attacks of breathlessness in the past 12 months in binary multivariable logistic regression in subjects with physician-diagnosed asthma, and in child-diagnosed and adult-diagnosed asthma.

	Physician-diagnosed asthma N=773		Child-diagnosed asthma N=325		Adult-diagnosed asthma N=448	
	OR (CI)	P	OR (CI)	P	OR (CI)	P
Female	1.49 (1.07-2.08)	**0.018**	1.62 (0.99-2.66)	0.055	1.40 (0.88-2.25)	0.16
Family history of asthma	1.48 (1.07-2.04)	**0.018**	2.04 (1.23-3.35)	**0.005**	1.16 (0.74-1.81)	0.52
Smoking						
• Never	1		1		1	
• Current	1.17 (0.77-1.78)	0.46	1.19 (0.66-2.15)	0.55	1.13 (0.60-2.13)	0.70
• Ex	0.91 (0.62-1.33)	0.62	0.81 (0.44-1.49)	0.50	0.95 (0.57-1.56)	0.82
Occupational exposure to VGDF	1.25 (0.88-1.77)	0.21	1.24 (0.73-2.11)	0.43	1.18 (0.74-1.89)	0.49
Living in rural area in childhood	1.05 (0.70-1.56)	0.82	0.82 (0.45-1.48)	0.51	1.27 (0.72-2.23)	0.40
Living on a farm in childhood	1.19 (0.75-1.90)	0.46	1.54 (0.70-3.36)	0.28	1.10 (0.60-2.01)	0.77
BMI						
• <24,99	1		1		1	
• 25-29,99	0.94 (0.65-1.37)	0.75	0.81 (0.46-1.44)	0.48	0.96 (0.57-1.59)	0.86
• 30-34,99	1.20 (0.75-1.91)	0.45	1.24 (0.63-2.44)	0.54	1.11 (0.57-2.17)	0.76
• >35	2.07 (0.93-4.59)	0.07	2.71 (0.64-11.51)	0.18	1.73 (0.65-4.60)	0.27
Adult-diagnosed asthma	2.41 (1.64-3.54)	**<0.001**	N/D		N/D	
Exercise <2 times per week	1.25 (0.88-1.79)	0.21	1.13 (0.68-1.88)	0.65	1.54 (0.90-2.61)	0.11
Allergic rhinitis	1.49 (1.07-2.09)	**0.019**	2.25 (1.33-3.79)	**0.002**	1.12 (0.71-1.75)	0.63
Age						
• 60-69	1		1		1	
• 50-59	1.12 (0.66-1.89)	0.67	0.47 (0.14-1.61)	0.23	1.48 (0.80-2.76)	0.22
• 40-49	0.76 (0.45-1.29)	0.31	0.48 (0.15-1.49)	0.20	0.75 (0.39-1.44)	0.39
• 30-39	0.76 (0.45-1.29)	0.31	0.50 (0.17-1.45)	0.20	0.71 (0.36-1.39)	0.32
• 20-29	1.30 (0.73-2.32)	0.37	0.75 (0.26-2.15)	0.60	2.13 (0.65-7.00)	0.21
COPD	2.02 (1.0-4.08)	0.052	1.15 (0.23-5.83)	0.87	2.37 (1.05-5.35)	**0.038**

5.5   Asthma remission (II)

Asthma was categorized as remitted in totally 162 (18,4%) subjects, and 150 of them also reported age at asthma diagnosis. The median time from asthma diagnosis was 19 years, and therefore the annual remission rate was 1.0/100/year for the whole study inspection period. Remission was most common in subjects with early-diagnosed asthma in both sexes, but more common in males in this age at diagnosis group than in females (p=0.006) (Figure 8).
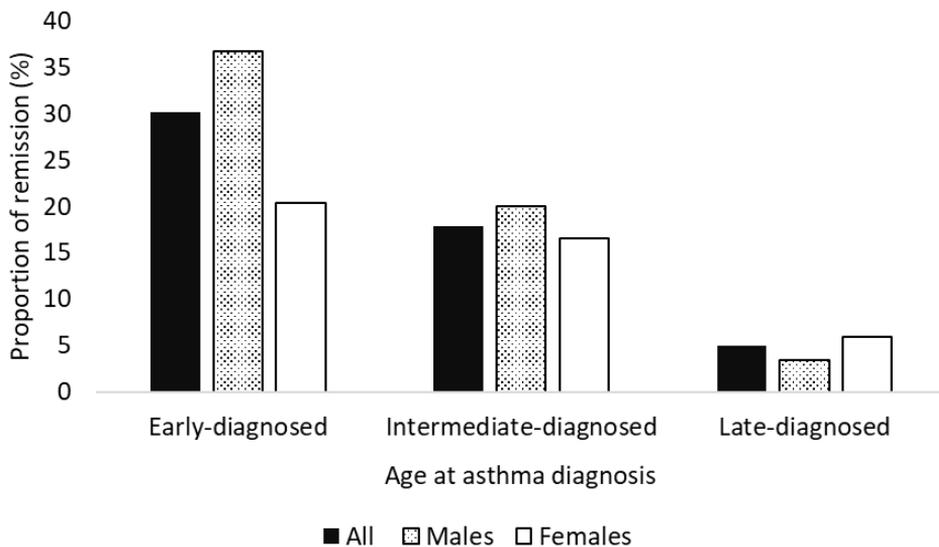
Figure 8.   Proportion of asthma remission in all subjects, males and females with physician-diagnosed asthma by age at diagnosis.

As analysed in 10-year groups, the lowest remission proportion was in subjects with age at asthma diagnosis at 40-49 years, in subjects which had 0-9 years' time from diagnosis and in subjects aged 60-69 years (Figure 9). Increasing age at asthma diagnosis had the highest effect size as association with asthma non-remission was investigated (OR=1.45, 1.32-1.58), as opposed to time from diagnosis (OR=1.33,

1.20-1.46) and age (OR=1.20, 1.09-1.32). Female gender (p=0.001), COPD (p<0.001), occupational exposure to VGDF (p=0.018), and family history of asthma (p=0.001) were also associated with non-remission of asthma in univariate analyses.
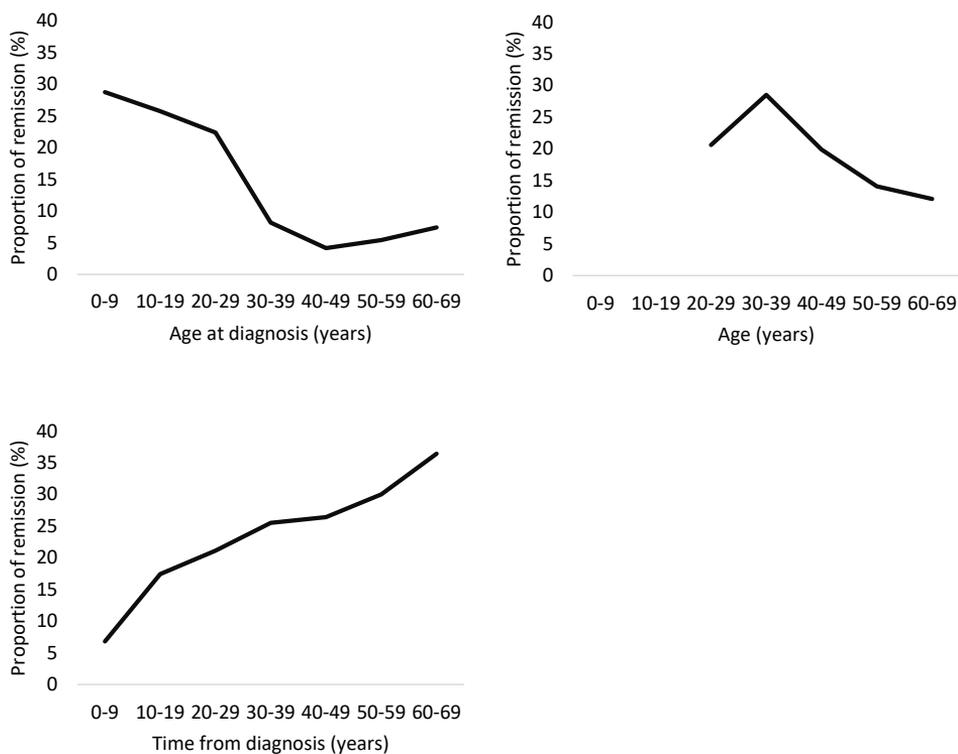
Figure 9. Remission of asthma by age at diagnosis, current age and time from asthma diagnosis.

5.6   Non-respiratory diseases in subjects with and without asthma (IV)

The most common non-respiratory disease in subjects without asthma (18.9%) and with late-diagnosed asthma (42.3%) was hypertension, and in early- (17.5%) and intermediate-diagnosed asthma (21.1%), obesity. As opposed to subjects without asthma, proportion of subjects with GERD and those with ≥1 non-respiratory diseases were more common in all these age at asthma diagnosis groups (p<0.001-0.018) (Table 7).

Table 7.   The risk of non-respiratory diseases in subjects with early-diagnosed, intermediate-diagnosed and late-diagnosed asthma compared to subjects without asthma in logistic regression analysis adjusted by age, sex, COPD, BMI and smoking. Without asthma was coded as 0 and in each regression analysis, and age at diagnosis group as 1.

	Early-diagnosed asthma (0-11 years)		Intermediate-diagnosed asthma (12-39 years)		Late-diagnosed asthma (40-69 years)	
	OR (CI)	P	OR (CI)	P	OR (CI)	P
Hypertension	1.37 (0.84-2.23)	0.20	1.12 (0.80-1.58)	0.51	1.30 (0.96-1.75)	0.09
Severe cardiovascular disease	1.02 (0.43-2.41)	0.97	0.91 (0.48-1.71)	0.76	1.28 (0.83-1.98)	0.26
Arrythmia	1.27 (0.67-2.39)	0.47	1.09 (0.68-1.76)	0.72	1.64 (1.11-2.41)	**0.012**
Stroke or TIA	1.81 (0.64-5.12)	0.27	1.74 (0.85-3.55)	0.13	1.43 (0.78-2.64)	0.25
Diabetes	0.73 (0.31-1.70)	0.46	1.05 (0.63-1.75)	0.85	1.41 (0.94-2.11)	0.10
Depression	1.00 (0.66-1.53)	0.98	1.45 (1.08-1.95)	**0.015**	1.74 (1.20-2.52)	**0.003**
Anxiety or panic disorder	1.01 (0.59-1.71)	0.98	1.85 (1.31-2.61)	**<0.001**	1.32 (0.78-2.21)	0.30
GERD	1.95 (1.18-3.24)	**0.009**	2.14 (1.48-3.08)	**<0.001**	2.80 (1.94-4.03)	**<0.001**
Sleep apnea	1.10 (0.50-2.43)	0.82	2.06 (1.23-3.43)	**0.006**	1.99 (1.23-3.20)	**0.005**
Osteoporosis	0.58 (0.078-4.24)	0.59	2.97 (1.69-5.22)	**<0.001**	2.41 (1.41-4.16)	**0.001**
Painful condition	1.23 (0.67-2.27)	0.50	1.64 (1.12-2.39)	**0.011**	2.05 (1.44-2.92)	**<0.001**
Number of non-respiratory diseases ≥1	1.44 (1.07-1.96)	**0.018**	1.63 (1.27-2.10)	**<0.001**	1.75 (1.23-2.48)	**0.002**
Number of non-respiratory diseases ≥2	1.22 (0.83-1.80)	0.32	1.64 (1.24-2.17)	**<0.001**	2.01 (1.48-2.72)	**<0.001**
Number of non-respiratory diseases ≥3	1.28 (0.73-2.23)	0.39	1.48 (1.02-2.15)	**0.038**	2.52 (1.82-3.49)	**<0.001**

Late-diagnosed asthma was more commonly associated with three or more non-respiratory diseases as opposed to subjects without asthma (p<0.001) or other age at asthma diagnosis groups (p=0.007) (Figure 10). In age-adjusted multivariable linear regression analysis, age at asthma diagnosis was positively associated with number of non-respiratory diseases (Unstandardized Beta=0.010, 0.002-0.017, p=0.008).
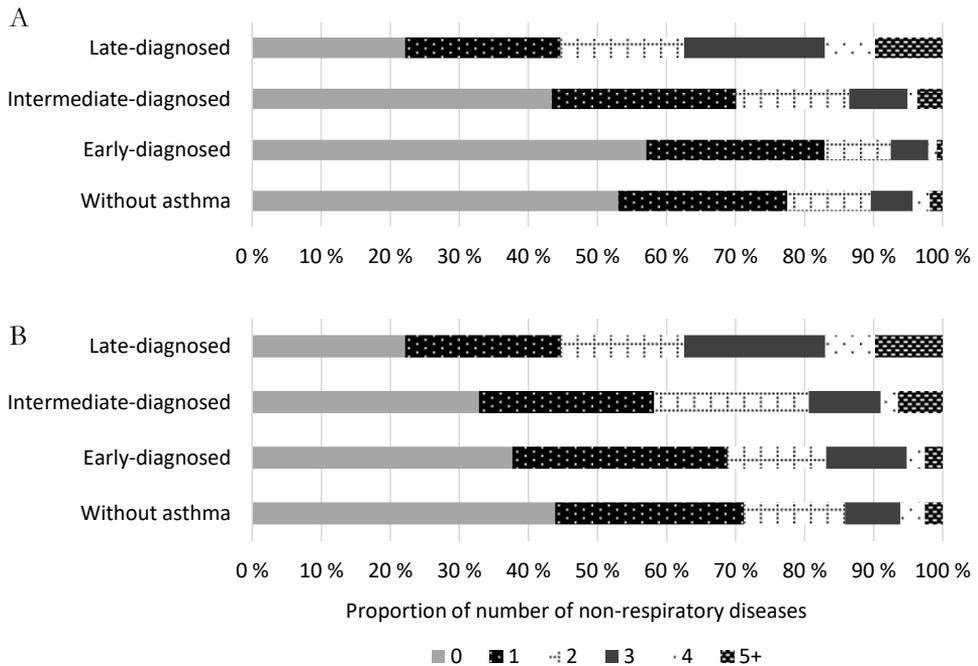
Figure 10. Number of non-respiratory diseases in subjects without asthma and with asthma by age at asthma diagnosis. In subfigure A in all subjects, and in B in subjects ≥40 years of age.

6   DISCUSSION

6.1   Summary of the most important results

The current study found that age at asthma diagnosis is not only an important but also a versatile modifier of asthma characteristics. Asthma diagnosed in adulthood was more difficult and common than child-diagnosed asthma. As asthma was diagnosed at adult age, it was more prone to be active, more symptomatic, and associated with more chronic non-respiratory diseases than asthma diagnosed in childhood. As age at diagnosis of asthma was higher, also the asthma incidence rate was higher, remission rate lower, and the number of associated comorbid diseases higher.

6.2   The results – comparative discussion and analysis of novelty

Age at asthma onset is repeatedly found as one of the most important characteristics which separates asthma by its clinical characteristics, phenotypes, and suggested endotypes[7,117]. However, the studies which take asthma age at onset into account have increased not until the recent years and are still uncomprehensive in many ways. In addition, age at asthma diagnosis has been considered in even more limited manners and study settings. Mostly the similar analyses to this study have been done with biased data which do not reflect the general population. Several of our analyses were of such that we have not seen similar analyses in previous literature. We discuss the matter more specifically as follows.

6.2.1   Asthma incidence by age at diagnosis (I)

Incidence of child-onset asthma in the population have been estimated previously in different cohort studies from USA, Australia, and The Netherlands to be

approximately 16-39/1000/year in 0-11-year-old children[67,153–155]. In contrast, a Finnish study utilizing asthma reimbursement registry requiring 6 months' usage of anti-inflammatory asthma medication, found the 0-9-year-old asthma incidence to be approximately 4/1000/year[1]. In our study, 0-9-year-old asthma incidence was 2,5/1000/year. These results demonstrate how diagnostic criteria in children, definition of asthma, study methods, and area of study make variations in the incidence rates, and how the data of ours are affected by cohort effect and centers to more clinically relevant asthma in childhood. In our data, remission in early-diagnosed (0-9 years) asthma was 30%, which is moderate in comparison to many previous estimates. This implies that our results most probably reflect childhood asthma which is most important to treat effectively.

Regarding adult asthma studies, rarely have they studied age-specific asthma incidence otherwise than dichotomously or been comprehensive in taking older aged adults into account[4,69]. A Finnish population cohort study found incidence of asthma medication reimbursements to be 1.0/1000/year in 15-20-year-olds and 2,1/1000/year in 36-38-year-olds[156]. Another, Swedish study reported incidence of 1.9/1000/year in 16-35-year-olds, 1.4/1000/year in 36-55-year-olds and 1.1/1000/year in 56-75-year-olds[72]. In our study, the incidence was similar as in these previous studies in 15-39-year-olds (1.8/1000/year pooled). However, we demonstrated a higher incidence of 2.7/1000/year in 40-59-year-olds, and 1.8/1000/year in 60-69-year-olds.

Differences in older age at diagnosis groups to the Swedish study are explained somewhat by that, they excluded ACO, and we did not. However, if we exclude ACO from our analyses, the corresponding incidences are 2.2/1000/year for 40-59 and 1.4/1000/year for 60-69-year-olds, therefore still higher. A Taiwanese study also found incidence to peak at 36-40 years of age (2.0/1000/year) similarly to our results[6], but even more our results are supported by another study from Finland which utilized asthma medication reimbursement rights[1]. This study found incidence to rise after 30 years of age especially in women, incidence rose up to oldest age groups (over 75 years of age), quite similarly to our findings. Otherwise, asthma incidence studies in subjects >70 years of age are very scarce.

Therefore, we find it appropriate that our age-specific asthma incidence reflects quite well the asthma in the population level, which is most important to identify and treat.

Furthermore, we described that in our unbiased population cohort, adult-diagnosed asthma comprised most asthma patients in females over 38 years and

males over 50 years of age. In a current report from Japan, elderly adults had reportedly later onset asthma more often than early-onset asthma[157], and in an US adult cohort, adult-onset asthma also became the dominant phenotype after middle age[63], however, their analysis did not include subjects over 50 years of age.

Furthermore, our analysis was in line with a recent Finnish study which reported adult-diagnosed asthma to become the dominant phenotype at 30-34 years of age in females and 50-54 years in males. Other similar analyses have not been reported previously to the best of our knowledge[1].

6.2.2   Asthma remission by age at diagnosis (II, III)

We quantified and compared adult asthma remission prevalence by age at asthma diagnosis. Most of previous studies have not looked age at asthma diagnosis as a continuous or non-dichotomous variable, or they have only included asthma with child or adult-diagnosis, not both, if specified[4,9,17,103,104,106,108].

One exception to this was an Italian study, which found remission rate to be 63% in subjects with age at asthma onset in 0-10 years, 40% in 10-20 years, and 15% in 20-44 years[4]. In our results, older age groups were also investigated, and the remission prevalence decreased by later age at asthma diagnosis up until 69 years of age. Another study from Sweden investigated 35-66-year-old adults[106]. Remission was 9% for 0-19 years, 6% for 20-39 years, and 4% for ≥40 years of age at asthma onset in that study. However, they did not for instance, report remission rate by age at asthma onset as a continuous variable, or by sex, which in our results was an important modifier of remission. In our results, overall remission by age at asthma diagnosis was 30% in 0-11, 18% in 12-39, and 5% in 40-69 years, so remission rates were higher than in the Swedish study but lower than in the Italian[4,106].

Asthma was defined differently in all the studies, the Swedish study demanded current asthma symptoms or medication use to be reported 10 years before the follow-up, and the Italian defined asthma by having ever asthma attack, not physician-diagnosis, whereas we defined asthma as ever having self-reported asthma diagnosis. Our results reflect ever physician-diagnosed asthma remission, different to the Swedish study, and are more precise by diagnosis of asthma compared to the Italian study.

The previously often described risk factors of asthma persistence or current asthma in childhood are reported to be lower lung function, allergic sensitization,

family history of asthma and female gender[109]. In contrast, in adult-onset asthma, non-remission or uncontrolled symptom burden have been associated with higher blood neutrophils, smoking, obesity, and rhinitis or nasal polyposis[10,104,108]. Our findings showed similarities and differences compared to previous studies.

Age at asthma diagnosis has not been used as a risk factor for remission rates in adjusted analyses in the past reports to the best of our knowledge. In adjusted analysis, the non-remission risk factors were family history of asthma, allergic rhinitis, female gender, and adult-diagnosed asthma, of which the latter also had the largest effect size. Age at asthma diagnosis also had the most important association with asthma remission compared to age, or time from diagnosis, which is a novel finding. These results imply that age at asthma diagnosis would be the most important basic patient characteristic to predict remission, and it should be reported in medical records and identified in clinical practice more readily than it used to be.

6.2.3   Asthma and comorbidities by age at diagnosis (IV)

Description and comparison of non-respiratory comorbid diseases of asthma by different age at asthma onset is a study aim very rarely seen in the literature previously. Even the subject of asthma and associative non-respiratory comorbid diseases has gained more interest just during the recent years. Most of the few previous studies assessing non-respiratory comorbidities and asthma age at onset, have assessed asthma in data gathered from specialized clinics, or in areas where the people are in a very unequal position in having possibilities to access healthcare services[135,140,142,149], and do not investigate the diseases versatilely assessing also the overall comorbid disease burden[140,142,149].

However, the same year as the IV was published, in fact very similar analysis was published investigating non-respiratory comorbid diseases by age at onset[158], but that study did not compare subjects with and without asthma such as in our analysis. In fact, we have not seen a study which would have investigated asthma comorbidities from this point of view.

In the aforementioned Dutch study, asthma was divided into three categories by age at onset: child-onset (0-18), adult-onset (18-40), and late-onset (>40 years of age)[158]. This was very similar to our division. In the age and sex-adjusted analyses, they found obesity to be more common in adult-onset than child-onset asthma, and similarly, DM, GERD, and obesity in late-onset than adult-onset asthma. In similar

adjusted analysis, we did not find any differences between the three age at diagnosis groups. Further, another recent clinical cohort study assessing difficult asthma did not find any associations between asthma age at diagnosis and non-respiratory comorbid diseases[135]. It must be noted that the Dutch study included over 550 000 subjects with asthma diagnosis from European health registries. Therefore, due to marked sample size, it must be considered if the statistically significant findings in the Dutch study are also clinically relevant and repeatable findings.

In our analyses, however, when we compared subjects categorized by age at asthma diagnosis, to subjects without asthma, we found significant associations between non-respiratory diseases and asthma, and the associations differed regarding, which age at asthma diagnosis group was assessed. In these analyses, the associations with chronic diseases were more frequent, and different for all three age at asthma diagnosis groups as opposed to subjects not having asthma, even when adjusted by basic and lifestyle characteristics known to associate with asthma and other diseases which could confound the results.

In addition, we were also able to assess the number of non-respiratory comorbidities as the study included versatile set of different common diseases. Later diagnosed asthma was associated with a higher number of non-respiratory diseases in adjusted analyses of our data. To the best of our knowledge, there were no previous studies which have assessed the association between age at asthma diagnosis and number of non-respiratory comorbid diseases, so this is also a novel finding.

6.3   Clinical and future research considerations

Asthma is a common disease and is estimated by GINA to encompass approximately 1% of the whole healthcare budget in developed countries nowadays, which is equivalent to diabetes or liver diseases[159]. Reporting high burden of respiratory symptoms in adulthood is also associated with higher mortality rate[160]. Previously it has been reported based on Finnish data that ≥65-year-old subjects use over one-third of all the hospital days used by asthma patients[161], and they also have the highest mortality from asthma[23].

According to the current study, most of these patients have adult-diagnosed asthma diagnosed later in life – more than 50% of over 44-year-old subjects had

asthma diagnosed after 40 years of age in this study. These patients have also higher prevalence of comorbid diseases as we reported from the current study[162].

Mostly adult and older adult subjects have comorbidities additionally to asthma, and in these situations, it is important to extract, which of the diseases account for poorer health outcomes or if the issue lies more in the multiple disease burden[163].

There are many reasons why asthma and other diseases would coexist and exacerbate each other. Asthma shares many risk factors and molecular mechanisms with other diseases, and some diseases may be influenced by longstanding asthma medication use, such as diabetes and osteoporosis[144]. Therefore, it is also important to avoid unnecessary asthma medication use.

It is estimated, that in severe asthma compared to non-severe asthma, over half of the incremental healthcare costs are due to comorbid conditions[164]. There is also evidence that at least type 2 diabetes, hypertension, and depression, as well as multimorbidity, have a negative impact on asthma control[126,129,146].

In addition, the current results implicate that patients with later onset asthma have minor tendency to remit with their asthma, and higher burden of asthma symptoms, and comorbidities. Therefore, especially they should be monitored in a more intense manner in long-term care, and due to simultaneous comorbidities, holistic approaches should be utilized in patient care, such as having hospitalists or generalist clinicians participating to asthma treatment or arranging multiprofessional team meetings as stepping from bench to bedside.

There are numerous longitudinal, clinical studies on asthma development and outcomes in children[15], but similar prospective studies in adults are few[107,165]. These and other methodologically versatile and high-quality studies would be important to implement in the future, considering different aged adults separately. Especially, longitudinal studies and outcomes on older adults with different onset ages of asthma, are needed to understand concrete needs of intensity of follow-up and early interventions.

Especially comorbid conditions and their interplay with asthma pathogenesis and clinical manifestation are widely overlooked in the current literature and clinical practice, in which medical specialties are nowadays very specific and polarized. This is though multimorbidity seems to be a marked and emerging, complex issue. Multimorbidity and its effect on asthma outcomes, and the clinical significance of different comorbid conditions in asthma should be investigated in future studies to find best approaches to treatment.

Finally, in the future age at asthma diagnosis should be recorded in a structured manner to patient registries in clinical practice due to its importance in the discussed matters. More healthcare resources should be directed to adult-diagnosed and especially late adult-diagnosed asthma in absolute and relative manner compared to child-diagnosed asthma.

6.4   Strengths and limitations of the study

6.4.1   Limitations and considerations of the study method

The study faces certain limitations most of which are related to the method of data acquisition. The most considerable potential limitation of this study is recall bias. However, studies have been made which evaluate the recall bias of retrospective reporting of age at asthma onset. Those studies have found that the reported onset ages are not unspecific, but rather a bit insensitive - the reported asthma cases are centered to more difficult asthma[50,52]. Therefore, it is most probable that the more clinically relevant asthma is validly reported in this study and as we know from the nature of asthma, especially milder asthma cases are very prone to misdiagnosis and may not have been asthma right from the beginning[41].

In addition, the study area (Finland) was ideal to limit recall bias. Since in Finland there is a governmental reimbursement system for asthma medication, the diagnoses are more accurate and easier to recall since the memory is tied to a financial benefit usually received 6 months from initial diagnosis. By unpublished data by Nurmi et al, in which a part of this study data were combined with national health register data, self-reported age at asthma diagnosis complied well with the register medication reimbursement data.

Another important limitation is the response bias. The response rate of this study was a little bit over 50 percent. This could lead to bias, such as exaggeration of asthma prevalence and symptom burden in the less respondent subgroups, such as younger males. In these subgroups, those who have asthma may have been more prone to respond in relation to other subgroups. Other studies have compared the early respondent to later respondent and non-respondent groups and found that responders are more often females and older, such as in this study. In addition, the

responders also have asthma more often. However, no studies which have investigated this topic, have concluded, that non-response affects the results markedly[71,166,167]. In addition, response rates have been around 50% in questionnaire studies quite widely for some time now, which as relatively estimated, means that the response rate was at a good level[166,167].

Other considerations include potential categorization of COPD patients as asthmatics as we did not exclude subjects with COPD in all the analyses and studied also older age groups. This was done to enhance generalizability of the results by limiting exclusions. Nevertheless, we widely did sensitivity analyses in which COPD patients were excluded to control this potential bias, and overall, very little changes to the key results took place. On the other hand, another limitation is that we did not include ≥ 70-year-old subjects. This oldest age group is severely understudied in asthma, but difficult to study with questionnaire studies for instance, as response reliability may decrease due to increased prevalence of disorders which cause dementia.

It should also be noted that the study method of retrospective view of asthma age at diagnosis in a wide age span in subjects makes it natural that the asthma cases reflect a long period during which diagnostic methods and criteria have changed. This is called cohort effect, which could be described more of a data characteristic than a bias.

After all, we consider that the study findings are consistent and mostly as marked, that weaknesses of the study methodology may affect the effect size of the most important findings, but not the direction of them.

6.4.2   Strengths

The major strengths of this study include the study sample, which was relatively large for a questionnaire study. In addition, we studied the general population with minimal exclusions, so that the generalizability of the results may be extended to the whole asthma population, not only to subpopulations. We also had a wide age range, and the study matter is rather difficult to approach prospectively due to the same reason, which makes the study inclusive. Thus, we had an optimal approach to study asthma by age at diagnosis in one data.

We had a professional international and multicentre research team consisting of clinical and research professionals, epidemiologists, and statisticians. Over 100

independent studies have been published from the FinEsS study, thus the current study methodology is quite well validated in practice by the scientific community. In addition, the study questionnaire was developed from the OLIN questionnaire, which is a modification from the BMRC questionnaire, which has utilized standardized approach in respiratory questionnaires[168,169].

Finland is an optimal location to study asthma in the population in the international context, due to a relatively equal public healthcare system, which is available to all Finnish individuals without private insurances. In Finland, a public governmental reimbursement system for asthma medication for all patients with asthma diagnosed with objective pulmonary function measuring, has been ongoing since 1970, and we have recently had comprehensive national programs to improve asthma identification and treatment in the primary healthcare called Asthma and Allergy Programs[1,60,161,170]. We have strong, up to date national formal guidelines in asthma and other important diseases diagnosis and management, in an open portal called Current Care Guidelines (Käypä Hoito)[171]. With these arguments, we believe, the principles of the study are quite as optimal as possible.

7 CONCLUSION

The main conclusions of the current study were the following:

Currently, asthma diagnosed at adult age is more prevalent than asthma diagnosed in childhood in the general Finnish adult population. Incidence of asthma peaked in males in early childhood, and in females in middle age. Adult-diagnosed asthma became the dominant phenotype of asthma in females by 38 years and in males by 50 years of age.

Asthma in adults was in remission more probably the earlier the asthma diagnosis was made – at under 11 years of age diagnosed asthma was remitted in 30%, at 12-39 years of age diagnosed in 17.2% and at 40-69 years of age diagnosed asthma in 5% of cases. In early childhood, asthma remission was more common in males than in females. Otherwise, remission proportion was quite consistent in both genders.

Adults with adult-diagnosed asthma had more asthma symptoms than adults with child-diagnosed asthma. The types of symptoms were also slightly different by age at asthma diagnosis.

Asthma was associated with a higher number of common chronic non-respiratory comorbidities the later the asthma diagnosis was made. The associated comorbid diseases were different by age at asthma diagnosis.

The current study enlightens how asthma burden is distributed in the general adult population - asthma diagnosed in adulthood, in many ways, has higher health burden than childhood-diagnosed asthma in adults and as compared to subjects without asthma. This study indicates that there are most probably important health benefits to be reached by applying more, well allocated resources to research, prevention, follow-up, and treatment of adult-diagnosed, and especially late adult-diagnosed asthma.

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Age- and gender-specific incidence of new asthma diagnosis from childhood to late adulthood

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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 a physician-diagnosis of asthma made at ≥ 18 years of age.

Results: Among those with physician-diagnosed 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 those with physician-diagnosed asthma 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.

1. 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 an 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 had 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 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.

2. Methods

2.1. 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 bilingual (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.

2.2. 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].

2.3. 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 < 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 1–20 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 the other analyses to allow comparison of the results with Helsinki FinEsS-data.

2.4. 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.

3. Results

3.1. Characteristics of responders and prevalence of asthma

Of the 8000 invited subjects, 4173 (52.3%) responded (Fig. 1). 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.

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 is reported in detail in the Online Repository.

3.2. 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
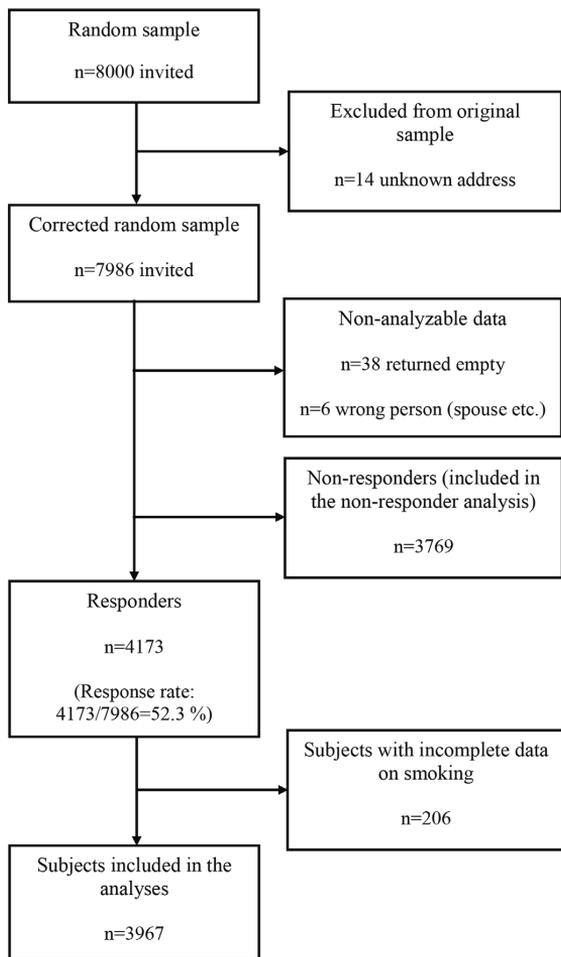
Fig. 1. Flow chart of the study.

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.

1946 to 2015 (see this article's Online Repository).

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

3.3. 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.

4. 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 of 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

age at diagnosis was 21 (IQR 7–43) years in men and 29 (IQR 15–44) years in women (p = 0.026). Altogether, 36.3% of subjects with physician-diagnosed asthma (31.9–41.0%) reported asthma diagnosis in childhood (< 18 years) and 63.7% (59.0–68.1%) in adulthood (≥18 years) (Fig. 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).

After excluding subjects who reported physician-diagnosed asthma but not the age at diagnosis (n = 18), incidence was calculated in 10-year age groups (Fig. 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

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.

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 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 a simple characterization new asthma 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-

Table 3

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

	Men, N = 1898 Physician-diagnosed asthma				P-value	Women, N = 2069 Physician-diagnosed asthma				P-value
	Yes N = 192		No N = 1706			Yes N = 253		No N = 1816		
Age (yrs), median (IQR)	50	(34–63)	54	(40–63)	0.023	52	(35–64)	52	(38–62)	0.972
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 (%)					< 0.001					< 0.001
	78	40.6	312	18.3		130	51.4	490	27.0	
Physician-diagnosed chronic bronchitis or COPD n (%)					< 0.001					< 0.001
	24	12.5	30	1.8		19	7.5	26	1.4	

BMI is based on responses of 1864 subjects in men and 2022 in women. IQR = interquartile range, SD = standard deviation.
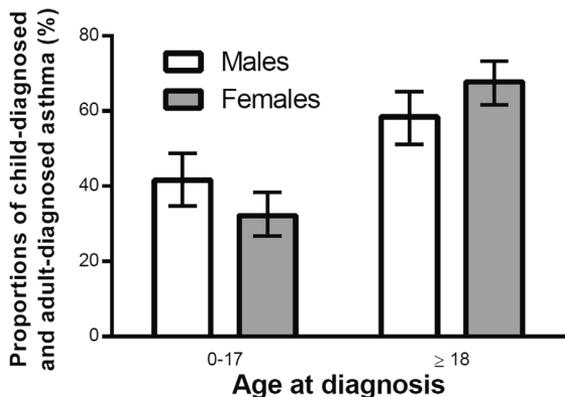
Fig. 2. Gender-specific proportions of asthma diagnosed during childhood and adulthood with 95% CI:s.
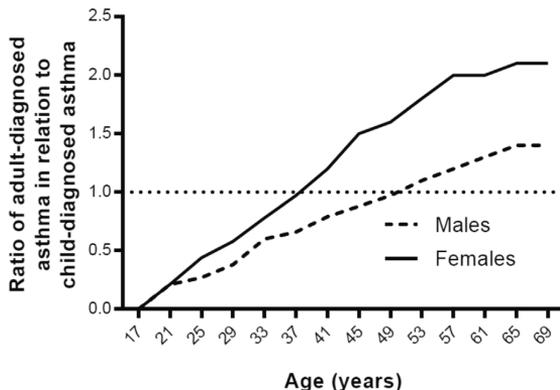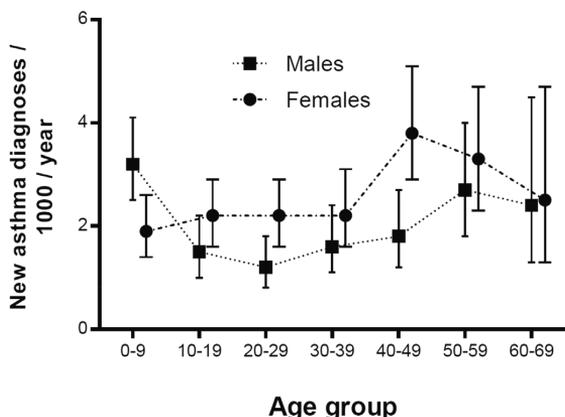

Fig. 3. Age- and gender-specific incidence rates of new asthma diagnosis with 95% CI:s.

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

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 the data from Helsinki. 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

Fig. 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.

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 non-response 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 ($\geq$ 70 years) are missing. Finally, due to the inclusion of subjects with significant smoking history, we have 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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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.rmed.2019.06.003.

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Declarations of interest

None.

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PUBLICATION
II

Asthma remission by age at diagnosis and gender in a population-based study

Honkamäki J, Piirilä P, Hisinger-Mölkänen H, Tuomisto LE, Andersén H, Huhtala H, Sovijärvi A, Lindqvist A, Backman H, Lundbäck B, Rönmark E, Lehtimäki L, Pallasaho P, Ilmarinen P, Kankaanranta H

Original Article

Asthma Remission by Age at Diagnosis and Gender in a Population-Based Study

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What is already known about this topic? Age of asthma onset differentiates patients in many ways. Remission is common in child-onset asthma, but seemingly less common in adult-onset asthma. Risk factors of asthma persistence from childhood to adulthood are well described.

What does this article add to our knowledge? In this study, age at asthma diagnosis after 40 years was the strongest risk factor of asthma nonremission, and age at diagnosis had a higher association with nonremission than current patient age or time from diagnosis.

How does this study impact current management guidelines? Age at asthma diagnosis should be highlighted in the guidelines as a key indicator of asthma prognosis. Adequate follow-up and research resource allocation should be provided for adult-onset, especially late adult-onset asthma.

BACKGROUND: Child-onset asthma is known to remit with high probability, but remission in adult-onset asthma is seemingly less frequent. Reports of the association between remission and asthma age of onset up to late adulthood are scarce.

OBJECTIVE: To evaluate the association between asthma remission, age at diagnosis and gender, and assess risk factors of nonremission.

METHODS: In 2016, a random sample of 16,000 subjects aged 20 to 69 years from Helsinki and Western Finland were sent a FinEsS questionnaire. Physician-diagnosed asthma was categorized by age at diagnosis to early- (0-11 years), intermediate- (12-39 years), and late-diagnosed (40-69 years) asthma. Asthma remission was defined by not having had asthma symptoms and not having used asthma medication in the past 12 months.

RESULTS: Totally, 8199 (51.5%) responded, and 879 reported physician-diagnosed asthma. Remission was most common in early-diagnosed (30.2%), followed by intermediate-diagnosed (17.9%), and least common in late-diagnosed asthma (5.0%)

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Abbreviations used
   BMI- Body mass index
     CI- Confidence interval
COPD- Chronic obstructive pulmonary disease
     OR- Odds ratio
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(P < .001), and the median times from diagnosis were 27, 18.5, and 10 years, respectively. In males, the corresponding remission rates were 36.7%, 20.0%, and 3.4%, and in females, 20.4%, 16.6%, and 5.9% (gender difference P < .001). In multivariable binary logistic regression analysis, significant risk factors of asthma nonremission were intermediate (odds ratio [OR] = 2.15, 95% confidence interval: 1.37-3.36) and late diagnosis (OR = 11.06, 4.82-25.37) compared with early diagnosis, chronic obstructive pulmonary disease (COPD) (OR = 5.56, 1.26-24.49), allergic rhinitis (OR = 2.28, 1.50-3.46), and family history of asthma (OR = 1.86, 1.22-2.85). Results were similar after excluding COPD. CONCLUSION: Remission was rare in adults diagnosed with asthma after age 40 years in both genders. Late-diagnosed asthma was the most significant independent risk factor for nonremission. © 2020 The Authors. Published by Elsevier Inc. on behalf of the American Academy of Allergy, Asthma & Immunology. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/). (J Allergy Clin Immunol Pract 2021;9:1950-9)

Key words: Asthma; Remission; Gender; Age of onset; Late-onset; Early-onset; Adult; Population study

Asthma is a chronic respiratory disease with a tendency to vary over time from more to less symptomatic periods and even remission. Remission is most accurately defined as an asymptomatic period of ≥12 months according to a recent consensus report,[1] and remitted asthma could also be considered as nonactive. Remission is noted as the most desirable, though difficult, but increasingly achievable treatment goal in both children and adults due to new treatment methods in asthma.[1]

A common symptom in children connected with childhood asthma is wheezing, which diminishes in approximately 75% of cases by mid-adulthood,[2-5] and mostly already by age 12 years.[6] Remission estimates in children vary noticeably by study methods: only 20% of asthma, which was objectively confirmed in early school-age remitted by age 19 years in Swedish data.[7] Furthermore, one-third of males but only a minority of females with persistent medication-dependent asthma diagnosed by age 19 years had remitted by 24 years of age in a recent Finnish nation-wide register study.[8] Severe asthma at baseline, female gender, and allergic sensitization are most often reported predictors of persistence of childhood asthma up to adult age.[2,3,5,7,9]

In contrast to child-onset asthma, only 3% to 17% of adult-onset asthma have remitted 5 to 25 years after the diagnosis.[10-19] As well as being more frequently persistent,[9] adult-onset asthma is more often associated with faster loss of lung function and poorer disease control than child-onset asthma.[13,20,21] In adults under 50 years of age, female gender, smoking, allergic sensitization, high body mass index (BMI), and increasing age are commonly reported risk factors of nonremission or more

inadequate control of asthma symptoms, without specific knowledge of asthma age of onset.[11,12,22-24] In addition, it seems that increasing age of onset would be a predisposing factor to persistence also later in adulthood.[14]

However, studies evaluating asthma remission have rarely been based on the general population or investigated remission according to age of onset. Although child- and adult-onset asthma have different characteristics,[20,25,26] adult-onset asthma is rarely divided and compared in early- and late-onset groups, even though they seem to be distinct.[27] Late-onset asthma (>40 years) has also been less studied. In addition, gender modifies asthma incidence, persistence, and severity.[7,8,22,23,28] Therefore, this study aimed to evaluate the association between age at asthma diagnosis, asthma remission, and gender, and to assess diagnosis-age specific risk factors of nonremission in an adult general population sample. We hypothesized that asthma diagnosed later in adulthood would be least often in remission, and risk factors of nonremission would differ according to age at diagnosis.

METHODS
Data acquisition and questionnaire

This study is a part of an international FinEsS (Finland, Estonia, Sweden) study. Totally, 16,000 subjects aged 20 to 69 years, 8000 from Helsinki and 8000 from South Ostrobothnia and Vaasa areas (Western Finland), were randomly selected by Statistics Finland in 10-year-age cohorts considering also gender distributions in the local populations. Subjects were sent a FinEsS respiratory questionnaire in February 2016, and in case of a nonresponse, up to 2 reminders were sent. A more detailed description of the methods has been published elsewhere.[28,29] The flowchart of data conformation is shown in Figure 1. Subjects with incomplete response to questions about smoking habits were excluded.

Definitions of key parameters

The commonly used variables in this study were defined as follows:

Physician-diagnosed asthma by the answer "yes" to the question "Have you been diagnosed by a doctor as having asthma?"

Age at asthma diagnosis "What age were you when asthma was diagnosed?"

Nonremitted asthma as physician-diagnosed asthma in combination with "yes" to at least 1 of the following questions: "Have you, during the last 12 months, had asthma symptoms (intermittent attacks or periodic breathlessness, with or without cough or wheezing/whistling in your chest)?" OR "Have you had wheezing or whistling in your chest at any time in the last 12 months?" OR "Do you currently use asthma medication (regularly or as needed)?"

Remission of asthma in ≥12 months by reporting physician-diagnosed asthma but not fulfilling criteria for nonremitted asthma.

Allergic rhinitis "Have you been diagnosed by a doctor as having allergic rhinitis caused by pollen (caused by, eg, birch, grass, mugwort)?" OR "Have you been diagnosed by a doctor as having other allergic rhinitis (caused by, eg, cat or dog)?"

Family history of asthma "Have any of your parents, brothers, or sisters now or previously had asthma?"

Area of habitat by participation to either the Helsinki or Western Finland sample.

COPD "Have you been diagnosed by a physician as having chronic bronchitis, chronic obstructive pulmonary disease (COPD), or emphysema?"

Occupational exposure "Does your working environment have now or has there previously been a lot of dusts, gases, or fumes?"

Living in rural area in childhood "Did you live on the countryside (not in a city or suburb) during your first 5 years of life?"

Living on a farm in childhood "Did you live on a farm during your first 5 years of life?"

Exercise per week "Exercise on your free time: How often do you exercise at least 30 minutes so that you are at least slightly short of breath and get sweaty?"

Diagnosis-age specific variables were defined by reporting physician-diagnosed asthma and concomitantly age at asthma diagnosis at:

0 to 11 years as *early-diagnosed asthma*,

12 to 69 years as *adult-diagnosed asthma*,

12 to 39 years as *intermediate-diagnosed asthma*, and

40 to 69 years of age as *late-diagnosed asthma*.

Remission was also evaluated in 10-year segments of diagnosis-age.

Statistical analyses

Statistical analyses were conducted with IBM SPSS Statistics version 25 (Armonk, NY). The χ^2 test was used in testing between categorical variables. In testing between dichotomous categorical and non-normally or normally distributed continuous variables, the Mann-Whitney and t-test were used, respectively. In testing between trichotomous categorical and non-normally or normally distributed variables, the Kruskal-Wallis test and 1-way analysis of variance were used, respectively. Normality in continuous variables was evaluated by visual inspection of distribution. A P value of <.05 was considered significant, and 95% confidence intervals (CIs) were reported.

Multivariable binary logistic regression was used to determine odds ratios (ORs) and CIs for asthma nonremission compared with remission, and to simultaneously adjust for potential confounding variables. Potential covariates were included in the model on the grounds of knowledge from previous studies, clinical experience, and significant association with the outcome variable. Covariates included in the final model were age at asthma diagnosis, BMI, age, gender, smoking, COPD, living in rural area in childhood, living on a farm in childhood, exercise per week, occupational exposure, allergic rhinitis, area of habitat, and family history of asthma. Relationships of continuous time-measuring variables (age, age at diagnosis, time from diagnosis) to asthma nonremission were investigated each separately by univariate binary logistic regression, to find out which of these variables had the strongest association with nonremission. The ORs were reported in 10-year segments of the time-measuring variables to clarify the result. Sensitivity analyses were conducted by excluding coexisting COPD and altering the remission definition by leaving out the criterion for asthma medication use.

RESULTS

Remission and age at diagnosis

Totally, 8199 subjects responded (51.5%). Basic responder data and characteristics of subjects with a nonresponse are reported elsewhere.[28,29] Responders with incomplete smoking data (N = 269) were excluded (Figure 1). After exclusion, 879 of 7930 subjects (11.1%) reported physician-diagnosed asthma. In 162 (18.4%) subjects, asthma was in remission, and in 19.9% if coexisting COPD was excluded. The median time from diagnosis was 19 years, and therefore the annual remission rate was 0.97/100/year. Demographics of subjects with remitted and nonremitted asthma are shown in Table I.

Age at asthma diagnosis was reported by 842 subjects with physician-diagnosed asthma. Subjects with early-diagnosed (0-11 years) asthma had the lowest BMI, and they were most often males and had most often allergic rhinitis as opposed to intermediate-diagnosed (12-39 years) and late-diagnosed (40-69 years) asthma. In contrast, subjects with late-diagnosed asthma had the highest BMI, they were mostly females, and only a third of them had allergic rhinitis (Table II). Remission was most common in early-diagnosed (30.2%), followed by intermediate-diagnosed (17.9%), and least common in late-diagnosed asthma (5.0%) (P < .001) (Figure 2, A). The median time from diagnosis was 27, 18.5, and 10 years, respectively, and the corresponding remission rates were 1.12/100/year, 0.97/100/year, and 0.50/100/year. If coexisting COPD was excluded, remission rates were 30.8%, 18.8%, and 6.2%, respectively.

Remission was further assessed by dividing age at asthma diagnosis into 10-year groups (Figure 2, B). A decrease in the proportion of remitted subjects was seen by increasing age at diagnosis: 22% to 29% of subjects with asthma diagnosed at 0 to 29 years of age were in remission, but if diagnosed at age 30 to 69 years, only 4% to 8% were in remission. When remission was further assessed in 10-year groups by current age, subjects aged 30 to 39 years had the highest (28.5%) and those aged 60 to 69 years had the lowest (12.1%) proportion of remission (Figure E1, available in this article's Online Repository at www.jaci-inpractice.org).

Risk factors of asthma nonremission

Adult-diagnosed (12-69 years) asthma (OR = 2.97, CI: 2.06-4.27) and both intermediate-diagnosed (12-39 years) (OR = 1.99, 1.35-2.92) and late-diagnosed (40-69 years) asthma (OR = 8.19, 4.31-15.55) (all P < .001) were significant risk factors of nonremission in relation to early-diagnosed asthma in a univariate binary logistic regression analysis. In addition, in 3 different univariate binary logistic regression analyses, the risk of nonremission was most strongly increased by age at asthma diagnosis (OR = 1.45, P < .001, per 10-year increase) compared with current age (OR = 1.20, P = .001, per 10-year increase) or time from diagnosis (OR = 1.33, P < .001, per 10-year decrease).

To further investigate the risk factors of asthma nonremission, we used multivariable binary logistic regression analysis, in which statistically significant risk factors of nonremitted asthma were intermediate or late diagnosis, coexisting COPD, allergic rhinitis, and family history of asthma. Female sex and current smoking showed tendency to increase risk of nonremission, and age, occupational exposure, living in a rural area in childhood, living on a farm in childhood, BMI, area of habitat, and exercise by week were not significantly associated with nonremission (Table III).

Independently analyzed, significant risk factors of non-remission in subjects with early-diagnosed asthma (0-11 years) were female gender and allergic rhinitis, and in adult-diagnosed asthma (12-69 years), family history of asthma, late-diagnosed asthma, and exercise ≥2 to 3 times per week, whereas coexisting COPD showed a high effect size (OR = 7.34) but was slightly insignificant (P = .055) probably due to insufficient data in the subgroup (Table III). Furthermore, if the medication usage criterion was left out of the definition of nonremission, and the
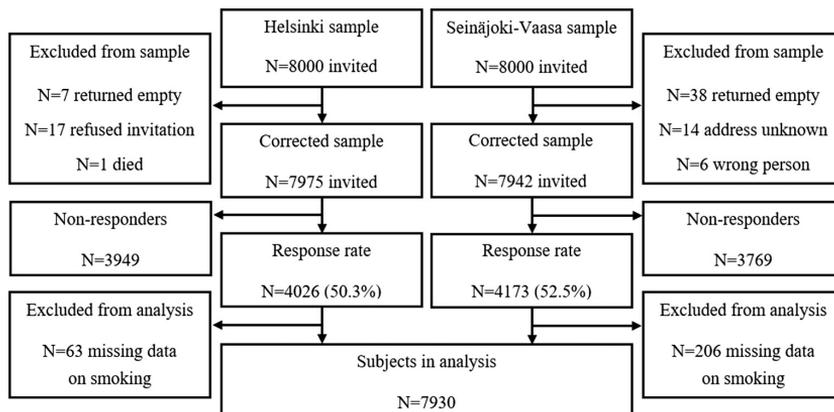
FIGURE 1. Flowchart of the study.

TABLE I. Demographics of subjects with physician-diagnosed asthma and comparison of remitted and nonremitted asthma

Variable	Physician-diagnosed asthma (N = 879)		Remitted asthma (N = 162)		Nonremitted asthma (N = 717)		P#
	Median	**Q₁-Q₃**	**Median**	**Q₁-Q₃**	**Median**	**Q₁-Q₃**	
Age (y)	47	32-61	39	31-56	49	33-61	**.001**
Age at diagnosis (y)*	23	10-40	12	6-22	28	12-43	**<.001**
Time from diagnosis (y)*	19	10-28	23	17-23	18	8-26	**<.001**
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**	
BMI†	26.7	5.3	26.2	4.6	26.9	5.4	.15
	N	**%**	**N**	**%**	**N**	**%**	
Female	498	56.7	72	44.4	426	59.4	**.001**
Family history of asthma	392	44.6	54	33.3	78	10.9	**.001**
Coexisting COPD	81	9.2	3	1.9	78	10.9	**<.001**
Smoking							.16
Never	409	46.5	29	17.9	179	25.0	
Current	208	23.7	53	32.7	209	29.1	
Ex	262	29.8	80	49.4	329	45.9	
Age at diagnosis (y)*							**<.001**
0-11	245	29.1	74	49.3	171	24.7	
12-39	358	42.5	64	42.7	294	42.5	
40-69	239	28.4	12	8.0	227	32.8	
Allergic rhinitis	508	57.8	84	51.9	424	59.1	.09
Living in rural area in childhood‡	406	46.7	67	41.4	339	47.9	.13
Living on a farm in childhood§	233	27.0	36	22.2	197	28.1	.13
Exercise ≥2-3 times per week‖	594	69.5	102	65.0	492	70.5	.16
Occupational exposure¶	335	39.3	49	31.0	286	41.2	**.018**
Helsinki as habitat	434	49.4	82	50.6	352	49.1	.73

BMI, Body mass index; *COPD*, chronic obstructive pulmonary disease; *Q₁-Q₃*, quartiles; *SD*, standard deviation.
Bolded text indicates statistical significance ($P < .05$).
Missing data: *37, †13, ‡10, §15, ‖24, ¶27.
#Measured by the χ^2 test in categorical variables, by the Mann-Whitney test in non-normally distributed continuous variables, and by the t-test in BMI.

definition was solely based on symptoms, exercise was no more a risk factor of nonremission, whereas other significant associations remained (Table E1, available in this article's Online Repository at www.jaci-inpractice.org).

A similar regression analysis was also conducted separately for intermediate- (12-39 years) and late-diagnosed (40-69 years) asthma. The only significant risk factor of nonremission in intermediate-diagnosed asthma (N = 328 in regression) was

TABLE II. Demographics and comparison of subjects with physician-diagnosed asthma categorized by age at asthma diagnosis

Variable	Early-diagnosed asthma (0-11 y) (N = 245)		Intermediate-diagnosed asthma (12-39 y) (N = 358)		Late-diagnosed asthma (40-69 years) (N = 239)		$P^{\#}$
	Median	Q_1-Q_3	Median	Q_1-Q_3	Median	Q_1-Q_3	
Age (y)	32	26-44	42	32-54	62	57-66	**<.001**
Time from diagnosis (y)*	27	20-39	19	10-28	10	4-17	**<.001**
	Mean	SD	Mean	SD	Mean	SD	
BMI†	25.6	4.8	26.5	5.2	28.1	5.4	**<.001**
	N	%	N	%	N	%	
Female	98	40.0	223	62.3	152	63.6	**<.001**
Family history of asthma	112	45.7	159	44.4	104	43.5	.89
Coexisting COPD	8	3.3	28	7.8	44	18.4	**<.001**
Smoking							**.002**
Never	124	50.6	172	48.0	98	41.0	
Current	68	27.8	80	22.3	49	20.5	
Ex	53	21.6	106	29.6	92	38.5	
Allergic rhinitis	174	71.0	228	63.7	85	35.6	**<.001**
Living in rural area in childhood‡	99	40.4	155	43.8	139	59.7	**<.001**
Living on a farm in childhood§	43	17.6	75	21.3	108	46.8	**<.001**
Exercise ≥2-3 times per week‖	165	67.9	248	71.5	160	69.6	.64
Occupational exposure¶	76	31.5	125	36.1	117	51.3	**<.001**
Helsinki as habitat	131	53.5	184	51.4	100	41.8	**.022**

BMI, Body mass index; *COPD*, chronic obstructive pulmonary disease; *Q_1-Q_3*, quartiles; *SD*, standard deviation.
Bolded text indicates statistical significance (*P* < .05).
Missing data: *37, †13, ‡10, §15, ‖24, ¶27.
#Measured by the χ^2 test in categorical variables, by the Kruskal-Wallis test in non-normally distributed continuous variables, and by 1-way analysis of variance in BMI.

exercise ≥2 to 3 times per week (OR = 2.29, 1.19-4.38, *P* = .013). Because the number of subjects in remission was very low in late-diagnosed asthma, risk factors of nonremission could not be reliably assessed. However, all the subjects who had coexisting COPD were not in remission.

As subjects with coexisting COPD were excluded to investigate its possible confounding effect, current smoking (OR = 1.84, 1.05-3.23, *P* = .033) became an additional significant risk factor of nonremission in physician-diagnosed asthma in similar regression analysis as in Table III (Table E2, available in this article's Online Repository at www.jaci-inpractice.org). The results remained mainly similar also regarding risk factors of adult-diagnosed asthma nonremission. In addition, if time from diagnosis was included as an additional covariate to the regression model, the association with late-diagnosed asthma remained statistically significant (Table E3, available in this article's Online Repository at www.jaci-inpractice.org).

Remission and gender

Based on previous knowledge of gender differences in asthma and a significant association between gender and asthma remission in this study, gender-specific remission was assessed. Of males, 23.6%, and of females, 14.5% were in remission (*P* = .001). Males and females in remission versus nonremission had lower age at asthma diagnosis, less often coexisting COPD and occupational exposure. Furthermore, males in remission versus nonremission were younger and had less often a family history of asthma (Table IV).

Males with early-diagnosed asthma were more frequently in remission than females (*P* < .006), but no significant difference was found in remission of intermediate- or late-diagnosed asthma between genders (Figure 3, *A*). Furthermore, when investigated in 10-year groups, a trend of decreasing remission by increasing diagnosis-age was seen in both genders (Figure 3, *B*). As diagnosed at 0 to 29 years of age, asthma was in remission in 27% to 35% of males and 20% to 23% of females, respectively. In contrast, if diagnosis was made in 30 to 69 years of age, corresponding percentages were 0% to 12% and 5% to 7%.

DISCUSSION

The primary result of this study was that remission of asthma became rarer as the age at diagnosis of asthma increased. The finding remained similar after adjusting by multiple confounding variables. Furthermore, age at diagnosis pooled in 10-year groups showed that any asthma diagnosed after age 30 years was prone not to be in remission in both genders.

The annual remission rate was 0.97/100/year in all subjects with physician-diagnosed asthma, 1.12/100/year in early-diagnosed, 0.97/100/year in intermediate-diagnosed, and 0.50/100/year in late-diagnosed asthma. The overall annual remission rate was similar to earlier reports,[11,17] but diagnosis-age centered remission rates have not been assessed previously, to the best of our knowledge. The cut-points of the diagnosis-age groups were chosen mainly based on asthma incidence switches[28] and cut-points used in the existing literature.[25] Particularly, age 40 years as a cut-point for adult-onset asthma has also been
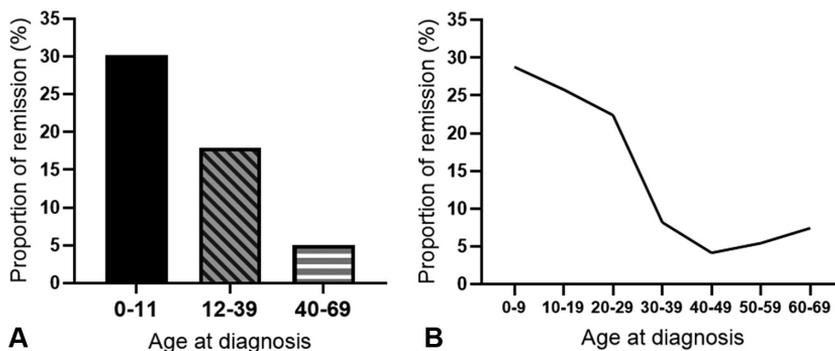
FIGURE 2. Remission (%) in subjects with physician-diagnosed asthma in groups defined by age at asthma diagnosis. In (**A**) is shown the proportion of remission in subjects with early (0-11), intermediate (12-39 years) and late-diagnosed (40-69 years) asthma. In (**B**) is shown the proportion of remission in subjects divided into 10-year groups by age at asthma diagnosis.

TABLE III. Risk factors of asthma nonremission compared with remission in subjects with physician-diagnosed asthma, and separately in subjects with early-diagnosed (0-11 years) and adult-diagnosed (12-69 years) asthma in multivariable binary logistic regression analysis*

Variable	Physician-diagnosed asthma (N = 773)		Early-diagnosed asthma (0-11 y) (N = 234)		Adult-diagnosed asthma (12-69 y) (N = 539)	
	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P
Female	1.47 (0.96-2.25)	.07	**2.39 (1.17-4.87)**	**.017**	1.07 (0.60-1.90)	.82
Family history of asthma	**1.86 (1.22-2.85)**	**.004**	1.77 (0.89-3.51)	.10	**1.78 (1.00-3.16)**	**.050**
Smoking						
Never	1		1		1	
Current	1.66 (0.96-2.87)	.068	1.48 (0.66-3.36)	.34	1.94 (0.85-4.43)	.11
Ex	0.99 (0.61-1.60)	.97	0.93 (0.40-2.14)	.86	1.19 (0.64-2.19)	.58
Occupational exposure	1.30 (0.83-2.04)	.26	1.43 (0.68-2.98)	.35	1.30 (0.71-2.38)	.39
Living in rural area in childhood	1.19 (0.69-2.05)	.52	1.46 (0.60-3.56)	.41	0.91 (0.44-1.87)	.79
Living on a farm in childhood	0.80 (0.44-1.46)	.47	0.85 (0.29-2.50)	.77	0.83 (0.39-1.78)	.64
BMI						
<24.99	1		1		1	
25-29.99	1.00 (0.62-1.60)	.99	0.84 (0.39-1.82)	.66	1.07 (0.57-2.03)	.83
30-34.99	0.92 (0.52-1.63)	.77	0.85 (0.34-2.15)	.74	0.92 (0.42-1.98)	.82
>35	1.84 (0.58-5.87)	.30	1.42 (0.18-11.48)	.74	2.30 (0.49-10.68)	.29
Age at diagnosis (y)			N/D			
0-11	1				1	
12-39	**2.15 (1.37-3.37)**	**.001**				
40-69	**11.08 (4.82-25.45)**	**<.001**			**5.04 (2.17-11.71)**	**<.001**
Exercise ≥2-3 times per week	1.34 (0.87-2.07)	.18	0.64 (0.31-1.30)	.22	**2.16 (1.20-3.87)**	**.010**
Allergic rhinitis	**2.29 (1.50-3.47)**	**<.001**	**4.89 (2.44-9.80)**	**<.001**	1.58 (0.89-2.80)	.12
Age (y)						
60-69	1		1		1	
50-59	1.40 (0.66-2.97)	.38	0.58 (0.13-2.59)	.48	1.86 (0.74-4.72)	.19
40-49	1.11 (0.54-2.31)	.78	0.81 (0.19-3.53)	.78	1.03 (0.42-2.48)	.96
30-39	0.97 (0.48-1.96)	.94	0.40 (0.11-1.49)	.17	1.34 (0.54-3.29)	.53
20-29	1.58 (0.75-3.31)	.23	0.78 (0.22-2.82)	.71	1.81 (0.63-5.17)	.27
Coexisting COPD	**5.56 (1.26-24.51)**	**.023**	1.66 (0.15-17.85)	.68	7.34 (0.96-56.19)	.055
Helsinki as habitat	0.98 (0.62-1.55)	.92	1.01 (0.48-2.15)	.97	0.99 (0.54-1.83)	.98

*BMI*, Body mass index; *CI*, confidence interval; *COPD*, chronic obstructive pulmonary disease; *OR*, odds ratio.
Bolded text indicates statistical significance ($P < .05$).
*Three different multiple logistic regression analyses were conducted with a target variable of remission of asthma. Nonremission was coded as 1 and remission as 0. Reported ORs have been adjusted for all the variables listed.

TABLE IV. Demographics of male and female subjects with physician-diagnosed asthma and comparison of gender-specific remitted and nonremitted asthma

	Males				Females			
Variable	Physician-diagnosed asthma (N = 381)	Remitted asthma (N = 90)	Nonremitted asthma (N = 291)	$P^{\#}$	Physician-diagnosed asthma (N = 498)	Remitted asthma (N = 72)	Nonremitted asthma (N = 426)	$P^{\#}$
	Median (Q_1-Q_3)	Median (Q_1-Q_3)	Median (Q_1-Q_3)		Median (Q_1-Q_3)	Median (Q_1-Q_3)	Median (Q_1-Q_3)	
Age (y)	44 (32-59)	36 (29-52)	46 (33-60)	**.004**	49 (33-61)	45 (32-59)	51 (33-62)	.09
Age at diagnosis (y)*	18 (6-35)	9 (5-19)	21 (8-40)	**<.001**	28 (14-43)	17 (10-25)	30 (15-45)	**<.001**
Time from diagnosis (y)*	20 (11-29)	24 (18-27)	18 (10-27)	**<.001**	18 (8-27)	23 (15-33)	17 (7-26)	**.001**
	Mean (SD)	Mean (SD)	Mean (SD)		Mean (SD)	Mean (SD)	Mean (SD)	
BMI†	27.1 (5.0)	26.6 (4.8)	27.2 (5.0)	.37	26.5 (5.5)	25.6 (4.4)	26.7 (5.6)	.15
	N (%)	N (%)	N (%)		N (%)	N (%)	N (%)	
Family history of asthma	154 (40.4)	25 (27.8)	129 (44.3)	**.005**	238 (47.8)	29 (40.3)	209 (49.1)	.17
Coexisting COPD	42 (11.0)	2 (2.2)	40 (13.7)	**.002**	39 (7.8)	1 (1.4)	38 (8.9)	**.028**
Smoking				.36				.21
Never	147 (38.6)	38 (42.2)	109 (37.5)		262 (52.6)	42 (58.3)	220 (51.6)	
Current	107 (28.1)	20 (22.2)	87 (29.9)		101 (20.3)	9 (12.5)	92 (21.6)	
Ex	127 (33.3)	32 (35.6)	95 (32.6)		135 (27.1)	21 (29.2)	114 (26.8)	
Age at diagnosis (y)*				**<.001**				**.002**
0-11	147 (39.8)	54 (64.3)	93 (32.6)		98 (20.7)	20 (30.3)	78 (19.2)	
12-39	135 (36.6)	27 (32.1)	108 (37.9)		223 (47.1)	37 (56.1)	186 (45.7)	
40-69	87 (23.6)	3 (3.6)	84 (29.5)		152 (32.1)	9 (13.6)	143 (35.1)	
Allergic rhinitis	219 (57.5)	48 (53.3)	171 (58.8)	.36	289 (58.0)	36 (50.0)	253 (59.4)	.14
Living in rural area in childhood‡	168 (44.7)	36 (40.0)	132 (46.2)	.31	238 (48.3)	31 (43.1)	207 (49.2)	.34
Living on a farm in childhood§	100 (26.6)	21 (23.3)	79 (27.6)	.42	133 (27.3)	15 (20.8)	118 (28.4)	.19
Exercise ≥2-3 times per week‖	236 (63.6)	54 (60.7)	182 (64.5)	.51	358 (74.0)	48 (70.6)	310 (74.5)	.49
Occupational exposure¶	190 (51.5)	36 (41.4)	154 (54.6)	**.031**	145 (30.0)	13 (18.3)	132 (32.0)	**.020**
Helsinki as habitat	189 (49.6)	43 (47.8)	146 (50.2)	.69	245 (49.2)	39 (54.2)	206 (48.4)	.36

BMI, Body mass index; *COPD,* chronic obstructive pulmonary disease; *Q_1-Q_3,* quartiles; *SD,* standard deviation.

Bolded text indicates statistical significance (*P* < .05).

Missing in males: *12, †3, ‡5, §5, ‖10, ¶12. Missing in females: *25, †10, ‡5, §10, ‖14, ¶15.

#Measured by the χ^2 test in categorical variables, by the Mann-Whitney test in non-normally distributed continuous variables, and by the *t*-test in BMI.
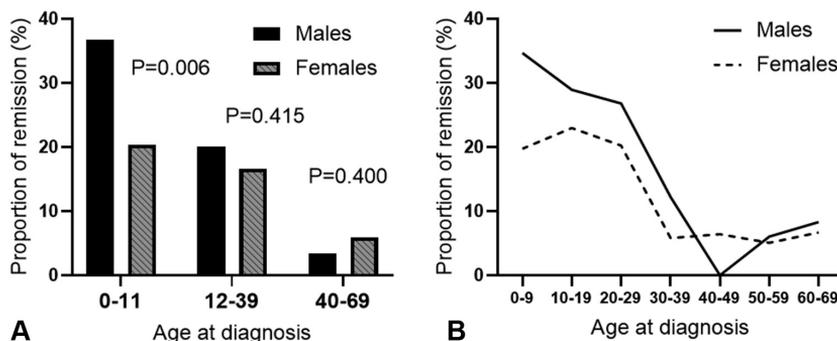
FIGURE 3. Gender-specific remission (%) in subjects with physician-diagnosed asthma in groups defined by age at asthma diagnosis. In (**A**) is shown the proportion of remission in subjects with early (0-11), intermediate (12-39 years) and late-diagnosed (40-69 years) asthma. In (**B**) is shown the proportion of remission in subjects divided into 10-year groups by age at asthma diagnosis.

previously proposed.[27] The remission definition we used adapted to a recent consensus report that argued ≥12 months to be the most optimal asymptomatic time frame to the definition of asthma remission.[1]

Early-diagnosed asthma (<12 years) was in remission in 30% of subjects: in 37% of males and 20% of females. Child-onset asthma is mostly defined similarly, as beginning at <12 years of age in other studies comparing asthma by age of onset.[25] Our remission estimates were low compared with studies with a symptom-based definition of asthma,[3] but very similar to studies that have included only physician-diagnosed or objectively confirmed asthma.[7,8] In addition, we found 2 risk factors of nonremission in early-diagnosed asthma: allergic rhinitis and female gender, similarly as in earlier reports.[3,7,9]

Intermediate-diagnosed asthma (12-39 years) was in remission in 17.9% of subjects, which settles between earlier findings.[11,30] The diagnosis-age definition in this group reflects quite well those of adult-onset or late-onset asthma in previous studies comparing asthma by age of onset because older subjects have been left out in most of them.[25,30] Interestingly, exercise ≥2 to 3 times per week was the only significant risk factor of non-remission in this group, which however lost its significance if subjects reporting current asthma medication use but not symptoms were considered as remitted. This suggests preventative medication usage in exercising subjects to explain the result. Other studies have similarly found only few risk factors of nonremission in subjects with similar diagnosis age: nasal polyps, allergic sensitization, worse lung function at baseline, inhaled corticosteroid use.[10,11,17,30] Daily physical activity has also been found to decelerate the loss of lung function in the long term in adult-onset asthma.[31]

Only 5% of subjects with late-diagnosed asthma were currently in remission. The result is in line with a previous prospective case-control study that reported remission rate by detailed diagnosis age in older age.[11] Our study was under-powered to determine risk factors of nonremitted late-diagnosed asthma, but all the subjects who had coexisting COPD were not in remission. Furthermore, remission was rarest in subjects aged 60 to 69 years, which could result from a higher proportion of worse-prognostic adult-diagnosed asthma in those with older age, but also from an increase in other comorbid conditions associated with age, which may play a role in asthma control.[32,33]

Comorbid COPD is reportedly a predisposing factor to poorer lung function in asthma,[34,35] but other comorbidities are also found to be more prevalent in patients with coexisting asthma and COPD than other patients with asthma.[34] Nevertheless, to the best of our knowledge, this was the first study to investigate risk factors of asthma nonremission by detailed asthma age of onset in adulthood and one of the few studies to investigate remission of asthma in the elderly population.

The 2 most remarkable independent risk factors of asthma nonremission were late-diagnosed asthma (OR = 11.1) and coexisting COPD (OR = 5.6). Exclusion of coexisting COPD did not affect the effect size or significance of late diagnosis (40-69 years) as a risk factor for nonremission, supporting its role as a real-life independent risk factor. Support for late diagnosis as a COPD-independent risk factor for poorer asthma prognosis is also provided in another study.[35] However, the effect size of late diagnosis age as a risk factor of asthma nonremission in an extensive stratified regression model has not been described earlier, to the best of our knowledge.

Current smoking transformed into a significant risk factor of asthma nonremission as subjects with coexisting COPD were excluded. Current smoking and smoking history are both indeed found to increase the risk of at least more difficult asthma.[36,37] Furthermore, BMI was not a significant risk factor of non-remission in any diagnosis-age group. High BMI was previously found to increase risk of more difficult asthma in a "dose-response" manner,[38] but another study, which also found an association between high BMI and more difficult asthma, showed that BMI and the actual remission of asthma were not associated,[11] consistent with this study.

In general, retrospective studies have limitations. Under-reporting mild asthma due to recall bias is found to be common[39] as well as misdiagnosis of asthma.[40] However, in Finland, the standard practice is to confirm asthma and COPD diagnoses with objective lung function tests highly recommended by Global Initiative for Asthma and the Finnish national health care guidelines, increasing the reliability of asthma diagnoses.[41,42] In addition, all citizens in Finland are covered by the National Health Insurance scheme and issued a personal health insurance card. This card is replaced usually 6 to 8 months from asthma diagnosis, containing not only asthma medication reimbursement information but also the replacement date. The card is

frequently used as medication is purchased. Thus, a considerable proportion of the respondents had verified data of their age at asthma diagnosis at hand when they filled the questionnaire. In addition, reimbursement of asthma medication[8] contributes a notable financial benefit to patients, which further enhances the memory related to precise diagnosis age, which was asked the study subjects with a well-validated questionnaire.[28]

Furthermore, in this study, a risk of misinterpretation of early-diagnosed asthma to adult-diagnosed asthma is present[43] as child-onset asthma may relapse after a long remission period in mid-adulthood.[4,5] However, subjects diagnosed in childhood are mostly allergic and males, whereas adult-diagnosed subjects mostly nonallergic and females,[20,28] therefore having different permanent characteristics. This also applied to our findings, suggesting that misinterpretation of early-onset relapsed asthma to adult-diagnosed asthma would not have caused a major bias. On the other hand, retrospective self-reported asthma age of onset assessment is previously found to be very specific.[39,44] For these reasons, we consider the reported asthma diagnoses in the present study to be precise and comprehensive, and only little misclassification of early-diagnosed asthma to late-diagnosed asthma or asthma to COPD in the older age groups. Therefore, although some mild asthma is probably left out, overall, we consider the reported asthma diagnoses in this study to be accurate.

Our data were based on an age-comprehensive cross-sectional random sample of general adult population: subjects were invited to the study with no exclusions, and all subjects who filled the questionnaire appropriately were included. In addition, the effect of nonresponse is previously discussed to be moderate in this study.[28,29] It should also be noted that cohort effect affects the results, as the oldest subjects had lived their childhood a long time ago, when asthma incidence was lower and identification more difficult. However, similar data would be very troublesome to collect prospectively. Furthermore, the data were based solely on the questionnaire, and clinical parameters were not available. Therefore, the evidence of distinguishing nonremitted and remitted asthma was not as accurate as in clinical data. However, clinical data are usually collected from secondary health care. Thus, we consider the results from these data accurate and generalizable to the primary health care patients as subjects conformed the general population.

As discussed, remission of asthma was lowest in subjects with later diagnosis age as has been reported earlier,[45] and the finding was parallel in both genders. In addition, it is shown that in adult subjects, current adult-onset asthma is more common than current child-onset asthma[8,28] and that adult-onset asthma predisposes to poorer response to traditional asthma medications, and uncontrolled asthma,[20] the mechanism being still unknown.[32,33] Taking all these findings into account, adult-onset asthma contributes a marked burden to the health care system altogether. What is also notable is that age of onset had the strongest association with asthma remission of the time-measuring variables in this study, which implicates that it would be a better factor to characterize asthma remission tendency than the age or duration of asthma of patients. In conclusion, to affect prognosis of asthma, follow-up resources should be increased in adult-onset asthma, and follow-up needs to be intensified especially in patients whose asthma has occurred after 30 years of age as they have the highest risk of nonremittance.

In conclusion, age at asthma diagnosis predicted well the probability of asthma remission through the age span. Adult-diagnosed asthma was rarely in remission, and even less often with increasing age at diagnosis. Gender did not seem to have a significant impact on remission of asthma diagnosed in adulthood. Age at diagnosis also defined the risk factors of non-remission, suggesting distinct differences between these phenotypes. More resources to adult-onset and especially late-onset adult asthma should be targeted, in terms of follow-up as well as in research, especially to unravel novel targets for more effective prevention or treatment methods.

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ONLINE REPOSITORY

As similar regression analysis with a similar definition of nonremission as in Table E1 was conducted separately for intermediate- (12-39 years) and late-diagnosed (40-69 years) asthma, no significant risk factors of nonremission were found in intermediate-diagnosed (12-39 years) asthma. Because the number of subjects in remission was very low in late-diagnosed asthma, risk factors of nonremission could not be reliably assessed.
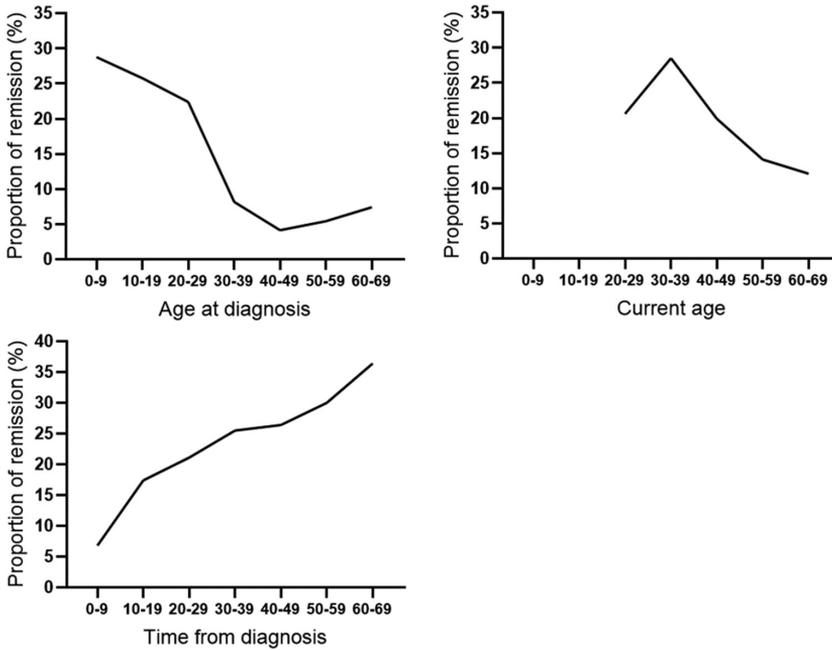
FIGURE E1. Remission (%) in subjects with physician-diagnosed asthma in relation to age at asthma diagnosis, current age, and time from diagnosis in 10-year categories.

TABLE E1. Risk factors of asthma nonremission compared with remission in subjects reporting physician-diagnosed asthma and separately in subjects with early-diagnosed (0-11 years) and adult-diagnosed (12-69 years) asthma in multivariable binary logistic regression analysis as the criterion of reporting not using asthma medication was removed from the definition of asthma remission *

Variable	Physician-diagnosed asthma (N = 773)		Early-diagnosed asthma (0-11 y) (N = 234)		Adult-diagnosed asthma (12-69 y) (N = 539)	
	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P
Female	1.20 (0.84-1.71)	.32	2.01 (1.05-3.86)	.035	0.94 (0.60-1.47)	.78
Family history of asthma	**1.74 (1.23-2.46)**	**.002**	1.64 (0.87-3.08)	.13	**1.69 (1.10-2.61)**	**.017**
Smoking						
Never	1		1		1	
Current	1.36 (0.86-2.13)	.19	1.07 (0.51-2.25)	.87	1.52 (0.82-1.81)	.18
Ex	0.87 (0.59-1.30)	.50	0.93 (0.42-2.05)	.86	0.87 (0.54-1.39)	.55
Occupational exposure	**1.46 (1.01-2.12)**	**.046**	1.83 (0.92-3.67)	.09	1.38 (0.88-2.18)	.16
Living in rural area in childhood	1.28 (0.82-2.00)	.28	1.42 (0.63-3.21)	.39	1.19 (0.68-2.08)	.55
Living on a farm in childhood	0.90 (0.55-1.48)	.68	0.85 (0.32-2.27)	.74	0.96 (0.52-1.75)	.88
BMI						
<24.99	1		1		1	
25-29.99	1.26 (0.85-1.87)	.25	1.11 (0.54-2.29)	.78	1.32 (0.81-2.13)	.27
30-34.99	1.44 (0.88-2.37)	.15	0.94 (0.40-2.21)	.88	1.72 (0.91-3.25)	.10
>35	2.32 (0.96-5.59)	.062	2.17 (0.30-15.89)	.45	2.63 (0.95-7.30)	.064
Age at diagnosis (y)						
0-11	1		N/D			
12-39	**1.63 (1.09-2.43)**	**.017**			1	
40-69	**3.41 (1.85-6.27)**	**<.001**			**2.06 (1.15-3.69)**	**.016**
Exercise ≥2-3 times per week	1.02 (0.71-1.49)	.91	0.56 (0.29-1.09)	.09	1.34 (0.84-2.15)	.22
Allergic rhinitis	**1.69 (1.19-2.42)**	**.004**	**3.50 (1.80-6.82)**	**<.001**	1.35 (0.87-2.10)	.22
Age (y)						
60-69	1		1		1	
50-59	1.36 (0.76-2.42)	.30	0.54 (0.13-2.33)	.41	1.64 (0.86-3.15)	.14
40-49	1.04 (0.57-1.89)	.91	0.45 (0.11-1.80)	.26	1.12 (0.56-2.26)	.75
30-39	0.99 (0.54-1.78)	.96	0.41 (0.12-1.46)	.17	1.12 (0.55-2.31)	.75
20-29	1.65 (0.88-3.11)	.12	0.71 (0.21-2.45)	.59	1.85 (0.79-4.37)	.16
Coexisting COPD	2.18 (0.98-4.85)	.057	2.51 (0.26-24.23)	.43	1.96 (0.83-4.63)	.12
Helsinki as habitat	1.04 (0.71-1.51)	.86	1.29 (0.64-2.59)	.48	1.00 (0.62-1.59)	.99

BMI, Body mass index; *CI*, confidence interval; *COPD*, chronic obstructive pulmonary disease; *OR*, odds ratio.

Bolded text indicates statistical significance ($P < .05$).

*Three different multiple logistic regression analyses were conducted with a target variable of remission of asthma. Nonremission was coded as 1 and remission as 0. Reported ORs have been adjusted for all the variables listed.

TABLE E2. Risk factors of asthma nonremission compared with remission in subjects with physician-diagnosed asthma and adult-diagnosed (12-69 years) asthma in multivariable binary logistic regression analysis as coexisting COPD was excluded*

Variable	Physician-diagnosed asthma, COPD excluded (N = 707)		Adult-diagnosed asthma (12-69 y), COPD excluded (N = 481)	
	OR (95% CI)	P	OR (95% CI)	P
Female	1.41 (0.92-2.16)	.12	1.02 (0.57-1.82)	.96
Family history of asthma	**1.93 (1.26-2.96)**	**.003**	1.74 (0.98-3.10)	.060
Smoking		**.033**		.07
Never	1	.95	1	.62
Current	**1.84 (1.05-3.23)**		2.20 (0.94-5.19)	
Ex	0.98 (0.61-1.59)		1.17 (0.63-2.16)	
Occupational exposure	1.20 (0.76-1.89)	.43	1.20 (0.65-2.19)	.56
Living in rural area in childhood	1.26 (0.72-2.18)	.42	0.98 (0.47-2.05)	.95
Living on a farm in childhood	0.77 (0.42-1.41)	.40	0.77 (0.36-1.67)	.51
BMI		.87		.98
<24.99	1	.61	1	.66
25-29.99	0.96 (0.60-1.55)	.35	1.01 (0.53-1.91)	.36
30-34.99	0.86 (0.48-1.53)		0.84 (0.39-1.82)	
>35	1.74 (0.54-5.62)		2.05 (0.44-9.57)	
Age at diagnosis (y)		**.001**		**<.001**
0-11	1	**<.001**		
12-39	**2.20 (1.40-3.46)**		1	
40-69	**11.48 (4.93-26.72)**		**4.87 (2.07-11.43)**	
Exercise ≥2-3 times per week	1.34 (0.86-2.07)	.19	**2.03 (1.13-3.67)**	**.019**
Allergic rhinitis	**2.34 (1.53-3.57)**	**<.001**	1.54 (0.86-2.75)	.15
Age (y)				
60-69	1		1	
50-59	1.55 (0.72-3.35)	.27	2.12 (0.81-5.56)	.13
40-49	1.12 (0.54-2.35)	.76	0.99 (0.41-2.41)	.98
30-39	0.98 (0.48-1.99)	.95	1.28 (0.52-3.17)	.60
20-29	1.68 (0.79-3.57)	.17	1.75 (0.61-5.04)	.30
Helsinki as habitat	0.96 (0.60-1.53)	.85	0.93 (0.50-1.73)	.82

BMI, Body mass index; *CI*, confidence interval; *COPD*, chronic obstructive pulmonary disease; *OR*, odds ratio.

Bolded text indicates statistical significance ($P < .05$).

*Two different multiple logistic regression analyses were conducted with a target variable of remission of asthma. Nonremission was coded as 1 and remission as 0. Reported ORs have been adjusted for all the variables listed.

TABLE E3. Risk factors of asthma nonremission compared with remission in subjects with physician-diagnosed asthma in multivariable binary logistic regression analysis as time from diagnosis variable was included, and in addition as coexisting COPD was excluded*

Variable	Physician-diagnosed asthma (N = 773)		Physician-diagnosed asthma, COPD excluded (N = 707)	
	OR (95% CI)	P	OR (95% CI)	P
Female	1.47 (0.96-2.24)	.077	1.41 (0.92-2.16)	.12
Family history of asthma	**1.88 (1.23-2.87)**	**.004**	**1.95 (1.27-3.00)**	**.002**
Smoking				
Never	1		1	
Current	1.68 (0.97-2.90)	.066	**1.85 (1.05-3.26)**	**.033**
Ex	0.99 (0.62-1.61)	.98	0.99 (0.61-1.60)	.95
Occupational exposure	1.28 (0.81-2.01)	.29	1.18 (0.75-1.87)	.47
Living in rural area in childhood	1.17 (0.68-2.02)	.57	1.23 (0.71-2.15)	.46
Living on a farm in childhood	0.80 (0.44-1.45)	.46	0.76 (0.42-1.40)	.38
BMI				
<24.99	1		1	
25-29.99	1.02 (0.63-1.64)	.95	0.98 (0.60-1.58)	.92
30-34.99	0.91 (0.51-1.62)	.75	0.86 (0.48-1.53)	.61
>35	1.84 (0.58-5.87)	.30	1.73 (0.54-5.58)	.36
Age at diagnosis (y)				
0-11	1		**1**	
12-39	1.67 (1.00-2.81)	.052	**1.77 (1.05-3.00)**	**.033**
40-69	**6.23 (2.25-17.29)**	**<.001**	**7.04 (2.49-19.87)**	**<.001**
Time from asthma diagnosis (y)				
≥20	1		1	
10-19	1.21 (0.69-2.13)	.51	1.11 (0.63-1.97)	.71
0-9	**2.29 (1.04-5.04)**	**.039**	2.10 (0.95-4.63)	.067
Exercise ≥2-3 times per week	1.40 (0.91-2.17)	.13	1.38 (0.89-2.15)	.15
Allergic rhinitis	**2.38 (1.56-3.63)**	**<.001**	**2.42 (1.58-3.71)**	**<.001**
Age (y)				
60-69	1		1	
50-59	1.27 (0.59-2.73)	.54	1.43 (0.65-3.12)	.38
40-49	0.92 (0.43-1.97)	.84	0.96 (0.44-2.06)	.91
30-39	0.76 (0.35-1.62)	.47	0.79 (0.37-1.70)	.55
20-29	1.05 (0.42-2.61)	.91	1.21 (0.48-3.06)	.68
Coexisting COPD	**5.35 (1.22-23.48)**	**.026**	N/D	
Helsinki as habitat	0.99 (0.62-1.57)	.95	0.97 (0.60-1.55)	.89

BMI, Body mass index; *CI*, confidence interval; *COPD*, chronic obstructive pulmonary disease; *OR*, odds ratio.
Bolded text indicates statistical significance (*P* < .05).
*Two different multiple logistic regression analyses were conducted with a target variable of remission of asthma. Nonremission was coded as 1 and remission as 0. Reported ORs have been adjusted for all the variables listed.

PUBLICATION
III

Age at asthma diagnosis is related to prevalence and characteristics of asthma symptoms

Hisinger-Mölkänen H, Honkamäki J, Kankaanranta H, Tuomisto L, Backman H, Andersen H, Lindqvist A, Lehtimäki L, Sovijärvi A, Rönmark E, Pallasaho P, Ilmarinen P, Piirilä P

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Age at asthma diagnosis is related to prevalence and characteristics of asthma symptoms

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ABSTRACT

Background: Although asthma may begin at any age, knowledge about relationship between asthma age of onset and the prevalence and character of different symptoms is scarce.

Objectives: The aim of this study was to investigate if adult-diagnosed asthma is associated with more symptoms and different symptom profiles than child-diagnosed asthma.

Methods: A FinEsS postal survey was conducted in a random sample of 16 000 20-69-year-old Finnish adults in 2016. Those reporting physician-diagnosed asthma and age at asthma diagnosis were included. Age 18 years was chosen to delineate child- and adult-diagnosed asthma.

Results: Of responders (N = 8199, 51.5%), 842 (10.3%) reported asthma diagnosis. Adult-diagnosed asthma was reported by 499 (59.3%) and child-diagnosed by 343 (40.7%). Of responders with adult-diagnosed and child-diagnosed asthma, 81.8% versus 60.6% used asthma medication (p < 0.001), respectively. Current asthma was also more prevalent in adult-diagnosed asthma (89.2% versus 72.0%, p < 0.001). Risk factors of attacks of breathlessness during the last 12 months were adult-diagnosis (OR = 2.41, 95% CI 1.64-3.54, p < 0.001), female gender (OR = 1.49, 1.07-2.08, p = 0.018), family history of asthma (OR = 1.48, 1.07-2.04, p = 0.018) and allergic rhinitis (OR = 1.49, 1.07-2.09, p = 0.019). All the analysed asthma symptoms, except dyspnea in exercise, were more prevalent in adult-diagnosed asthma in age- and gender-adjusted analyses (p = 0.032-<0.001) which was also more often associated with 5 or more asthma symptoms (p < 0.001) and less often with non-symptomatic appearance (p < 0.001) than child-diagnosed asthma.

Conclusion: Responders with adult-diagnosed asthma had more often current asthma and a higher and multiform asthma symptom burden, although they used asthma medication more often compared to responders with child-diagnosed asthma.

Keywords: Asthma, Age of onset, Symptom, Population study, Late-onset

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INTRODUCTION

Asthma may occur at any age, and it varies from very symptomatic to mild or symptom-free. According to earlier research, age at asthma diagnosis may influence asthma burden and prognosis.[1-4] Adult-diagnosed asthma has been reported to be more often related to environmental and lifestyle factors compared to child-diagnosed asthma, which again is frequently associated with atopy and genetic factors.[2-5] Furthermore, adult-onset asthma has been reported to be associated with poorer treatment response and prognosis,[2,6] inferior lung function,[7] weaker working ability,[8] and non-remission[9-11] more often than child-onset asthma, which usually has a good prognosis and high probability to remit.[2,12,13] Though these differences have been proposed, studies unravelling the role of age at asthma diagnosis in general population samples are still scarce.[3,10,14,15]

Common symptoms of asthma are wheezing, shortness of breath, and cough. Reporting multiple asthma symptoms is associated with decreased lung function, increased airway inflammation, and bronchial hyperresponsiveness, reflecting uncontrolled and difficult asthma.[16,17] Insufficient medication adherence, poor inhaler technique, and comorbidities may worsen asthma control and lead to difficult-to-treat asthma. If these issues have been addressed and the symptom burden is still marked, asthma is considered severe.[18] Severe asthma may reportedly begin in childhood or adulthood, but the molecular findings of bronchial inflammation seem to differentiate between them, more symptomatic disease associating especially with eosinophilic bronchial inflammation.[3,19,20]

Most of the few studies on asthma symptom burden between early- and late-onset asthma have resulted in only little or no difference.[3,4,19,21] This is in contrary to reported differences between child- and adult-diagnosed asthma severity and prognosis;[2,6,10,15] therefore, a deeper understanding of differences in asthma symptom burden in adults with asthma ever diagnosed by a physician stratified by age at asthma diagnosis is needed, especially in the population level. Therefore, firstly, we aimed to test our hypothesis that asthma diagnosed in adulthood differs in reported symptoms both in quantitative and qualitative manner from asthma diagnosed in childhood in a general adult population. Secondly, we aimed to investigate if the risk factors of having asthma symptoms differ in adults with asthma characterized by age at diagnosis.

MATERIAL AND METHODS

Study subjects

In 2016, a cross-sectional random sample of totally 16 000 20-69-year-old adults, 8000 from both Helsinki and Western Finland areas, were collected from the Statistics Finland. The sample was sent a FinEsS respiratory questionnaire with up to 2 reminders.

Study design

Detailed descriptions of the study methods and questionnaire and the complete Finnish FinEsS 2016 questionnaire are available elsewhere.[14,22]

The common variables were defined as follows.

Physician-diagnosed asthma. An affirmative answer to "Have you been diagnosed by a doctor as having asthma"?

Current asthma. Reporting *physician-diagnosed asthma* in combination with a positive answer to at least 1 of the following questions: (1) Have you had shortness of breath during the last 12 months, (2) Have you had any wheeze during the last 12 months, or (3) Do you currently use asthma medication.

Age at asthma diagnosis. "What age were you when asthma was diagnosed"?

Asthma diagnosis-age specific variables by reporting physician-diagnosed asthma and concomitantly age at diagnosis at.

0–17 years as child-diagnosed asthma and.

18–69 years as adult-diagnosed asthma.

Age 18 or 20 years is a frequently used cut-point in the age of asthma onset -studies.[3,14] It is also near the age when reimbursement right for asthma medication needs to be renewed in Finland (age 16 years) and when treatment of

asthma patients is shifted from pediatrics to pulmonology.

Asthma medication use. "Do you currently use asthma medication (permanently or as needed)"?

Expenses to asthma medication. The expenses were determined questionnaire-based in euros.

"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)"?

Chronic rhinitis. "Have you had longstanding nasal congestion" or "Have you had longstanding rhinitis"?

Family history of asthma. "Have any of your parents, brothers or sisters now or previously had asthma"?

Co-existing chronic obstructive pulmonary disease (COPD). "Have you been diagnosed as having chronic bronchitis, chronic obstructive pulmonary disease (COPD) or emphysema by a doctor"?

Occupational exposure to vapors, gases, dust, or funes (VGDF). "Does your working environment have now or has there previously been a lot of dusts, gases or fumes"?

"Did you live in the countryside (not in a city or suburb) during your first five years of life"?

Living on a farm in childhood. "Did you live on a farm during your first five years of life"?

Exercise per week. "Exercise in your free time: How often do you exercise at least 30 min so that you are at least slightly short of breath and get sweaty"?

Attacks of breathlessness. "Do you have now, or have you had asthma symptoms during the last 12 months (breathlessness with or without cough or wheezing)"?

Wheeze. "Have you had wheezing or whistling in your chest at any time in the last 12 months"?

Asthmatic wheeze. Reporting *wheeze* and affirmative responses to "Have you been at all breathless when the wheezing sound was present"? and "Have you had this wheezing or whistling when you did not have a cold"?

Longstanding cough. "Have you had a longstanding cough during the last 12 months"?

Sputum production. "Do you bring up phlegm on most days during periods of at least three successive months"?

Dyspnea in cold. "Do you usually have dyspnea or severe cough in cold weather"?

Dyspnea in exercise. "Do you usually have dyspnea or severe cough during exercise"?

Dyspnea mMRC≥2. "Do you have to walk slower than other people of your age because of dyspnea"?

Morning dyspnea. "Have you awakened with a feeling of tightness in your chest during the past 12 months"?

The *number of asthma symptoms* comprised of the following 8 symptoms: *wheeze, longstanding cough, sputum production, dyspnea in cold, dyspnea in exercise, dyspnea mMRC≥2, attacks of breathlessness,* and *morning dyspnea.*

Methods & analysis

Statistical analyses were conducted with SPSS Statistics version 25. To compare categorical groups, chi-square test was utilized. Similarly, when comparing normally and non-normally distributed continuous variables between two categorical variables, t-test and Mann-Whitney test were utilized, respectively. A p-value of <0.05 was considered statistically significant.

Multivariable binary logistic regression was used to determine independent associations between covariates and attacks of breathlessness in ≤12 months in odds ratios (OR) and 95% confidence intervals (CI). The covariates were included in the model by potential confounding effect measured by individual statistical associations with the outcome variable as well as previous knowledge from the literature and clinical experience.

Subjects with incomplete data on smoking habits were excluded from analyses. Sensitivity analyses were conducted by excluding subjects with co-existing COPD and by conducting analyses also only in responders with current asthma.

RESULTS

After 2 reminders, 51.5% (n = 8199) responded. Of responders, 10.3% (n = 842) reported an asthma diagnosis by a physician, and age at diagnosis. Responders with asthma were more often female than male, and their median age was 47 years. Almost every second patient (46.8%) was a never smoker, but 23.4% reported current smoking. Asthma medication use was reported by 73.2%. More comprehensive basic responder and non-responder analyses are reported elsewhere.[10,14,22]

Adult-diagnosed asthma was reported by 59.3% (n = 499) and child-diagnosed by 40.7% (n = 343) of responders. In adult-diagnosed asthma, allergic rhinitis (49.1% versus 70.6%, p < 0.001) was less frequent, and mean body mass index (BMI) was higher (27.4 versus 25.7, P < 0.001) compared to child-diagnosed asthma (Table 1). In addition, prevalence of current asthma was higher (89.2 versus 72.0%, p < 0.001), and expenses to asthma medication were higher in adult-diagnosed than child-diagnosed asthma (median 180 versus 50 euros, p < 0.001).

Different asthma symptoms by age at diagnosis are shown in Table 2 in all responders with asthma diagnosed by a physician. In age and gender-adjusted analysis, all the individually analysed symptoms, except dyspnea in exercise, were more prevalent in those with adult-diagnosis compared to those with child-diagnosis. In addition, the number of asthma symptoms was higher in adult-diagnosed asthma than child-diagnosed (median 4 versus 3 symptoms, p < 0.001). There were also significantly more responders with 5 or more reported asthma symptoms in responders with adult-diagnosis (p < 0.001) (Fig. 1).

To exclude the possibility that the differences in asthma symptoms would be due to co-existing COPD, which prevalence was 9.5% in subjects with ever having asthma diagnosed by a physician, we made sensitivity analysis by excluding co-existing COPD. As a result, only asthmatic wheeze and dyspnea mMRC≥2 lost their significance while all the other significant differences stayed the same (Supplementary Table 1). We also did a logistic regression analysis in which longstanding cough was the outcome variable and age, age at asthma diagnosis, hypertension,

coronary artery disease, heart failure, atrial fibrillation, and gastro-esophageal reflux disease independent variables. In this analysis, adult-diagnosed asthma was still significantly associated with longstanding cough (p < 0.001).

A gender disparity is reported in asthma,[23] and was present also in our results as male gender was more prevalent in child-diagnosed compared to adult-diagnosed asthma (p < 0.001). Therefore, we studied if asthma symptoms differentiated in age at asthma diagnosis defined groups between genders, and also if asthma symptoms differentiated in males and females by age at asthma diagnosis. Gender-specific differences in age-adjusted analyses were found in child-diagnosed asthma in dyspnea in cold, dyspnea in exercise, dyspnea mMRC≥2 and attacks of breathlessness. In adult-diagnosed asthma, significant findings were seen in wheeze, and dyspnea in cold (Table 3). All the symptoms with a statistically significant difference were more common in females, except wheeze in adult-diagnosed asthma in males. In males, more and stronger significant differences were found when asthma symptoms were analysed between child- and adult-diagnosed asthma.

As asthma remission is reportedly more common in child-diagnosed asthma,[2,11,13] we wanted to find out if the responders with remitted child-diagnosed asthma would explain the results and the comparisons were also performed in patients with current asthma. Demographics of responders with current asthma are reported in Supplementary Table 2. Longstanding cough and attacks of breathlessness were significantly more prevalent in adult-diagnosed current asthma (Fig. 2), and excluding co-existing COPD in current asthmatics did not change the result (data not shown). Reporting 8 asthma symptoms was more common in responders with adult-diagnosed current asthma than in child-diagnosed (p = 0.005) (Supplementary Fig. 1).

We also did an analysis of asthma symptoms in which asthma was categorized by age at diagnosis using age 60 years as the delineation point (Supplementary Table 3) and in adjusted analysis not any symptom prevalence differed between these age at diagnosis strata.

	All with physician-diagnosed asthma N = 842		Child-diagnosed asthma N = 343		Adult-diagnosed asthma N = 499		P
	med	Q₁-Q₃	med	Q₁-Q₃	med	Q₁-Q₃	
Age	47	32-61	33	26-43	56	44-64	<0.001
Age at diagnosis	23	10-40	8	4-12	38	27-49	<0.001
Years since diagnosis	19	10-28	25	18-36	14	6-23	<0.001
Expenses to asthma medication per year (€)ᵃ	100	20-230	50	0-100	180	70-300	<0.001
	mean	SD	mean	SD	mean	SD	
BMIᵇ	26.7	5.3	25.7	4.8	27.4	5.5	<0.001
	N	%	N	%	N	%	
Male	369	43.8	183	53.4	186	37.3	<0.001
Co-existing COPD	80	9.5	9	2.6	71	14.2	<0.001
Smoking							<0.001
• Never	394	46.8	176	51.3	218	43.7	
• Current	197	23.4	89	25.9	108	21.6	
• Ex	251	29.8	78	22.7	173	34.7	
Allergic rhinitis	487	57.8	242	70.6	245	49.1	<0.001
Chronic rhinitis	479	56.9	168	49.0	311	62.3	<0.001
Asthma medication use	616	73.2	208	60.6	408	81.8	<0.001
Current asthma	692	82.2	247	72.0	445	89.2	<0.001
Family history of asthma	375	44.5	153	44.6	222	44.5	0.973

(continued)

	All with physician-diagnosed asthma N = 842		Child-diagnosed asthma N = 343		Adult-diagnosed asthma N = 499		P
	med	Q₁-Q₃	med	Q₁-Q₃	med	Q₁-Q₃	
Living in rural area in childhood[c]	393	47.2	133	38.9	260	53.1	**<0.001**
Living on a farm in childhood[d]	226	27.3	59	17.3	167	34.4	**<0.001**
Exercise ≥2 times per week[e]	573	69.9	233	68.3	340	69.5	0.713
Occupational exposure to VGDF[f]	318	39.0	106	31.5	212	44.3	**<0.001**

Table 1. (Continued) Demographics of responders ever been diagnosed with asthma by a physician and of adult-diagnosed and child-diagnosed asthma strata and statistical comparison of the strata. *Statistical comparison between adult- and child-diagnosed asthma by chi-square test in categorical, t-test in normally and Mann-Whitney test in non-normally distributed continuous variables. Bolded text indicates a statistically significant P-value (P < 0.05). Missing:* ᵃ *= 231,* ᵇ *= 12,* ᶜ *= 10,* ᵈ *= 15,* ᵉ *= 22,* ᶠ *= 27. Abbreviations: BMI, Body Mass Index; COPD, Chronic Obstructive Pulmonary Disease; Med, Median; Q1-Q3, Quartiles; SD, Standard Deviation*

	All with physician-diagnosed asthma N = 842		Child-diagnosed asthma N = 343		Adult-diagnosed asthma N = 499		P[a]
	N	%	N	%	N	%	
Wheeze	452	53.7	158	46.1	294	58.9	**<0.001**
Longstanding cough	297	35.3	88	25.7	209	41.9	**<0.001**
Sputum production	257	30.5	75	21.9	182	36.5	**0.005**
Asthmatic wheeze	489	58.1	82	23.9	145	29.1	**0.032**
Dyspnea in cold	437	51.9	152	44.3	285	57.1	**0.009**
Dyspnea in exercise	444	52.7	162	47.2	282	56.5	0.084
Dyspnea mMRC≥2	228	27.1	52	15.2	176	35.3	**0.023**
Morning dyspnea	342	40.6	119	34.7	223	44.7	**0.003**
Attacks of breathlessness	552	65.6	183	53.4	369	73.9	**<0.001**

Table 2. Asthma symptoms in responders ever been diagnosed with asthma by a physician and in child-diagnosed and adult-diagnosed asthma strata, and statistical comparison of the strata *Statistical comparison between adult- and child-diagnosed asthma by chi-square test. ᵃAdjusted by age and gender. Bolded text indicates a statistically significant P-value (P < 0.05)*

As allergic asthma is more common among asthmatics diagnosed at younger age one could question whether the results seen in this study would be explained by different allergic status instead of age at diagnosis. Therefore, we did a linear regression analysis with the number of asthma symptoms as the dependant variable, and age, age at asthma diagnosis and physician-diagnosed allergic rhinitis as the independent variables. In this analysis, adult-diagnosed asthma had an odds ratio of 6.0 (p < 0.001) and physician-diagnosed allergic rhinitis 2.0 (p = 0.05).

Multivariable binary logistic regression analyses on the risk factors of attacks of breathlessness in the last 12 months in responders ever been diagnosed with asthma by a physician as well as in child and adult-diagnosed asthma are given in Table 4. Some responders had missing data in covariates included in the regression analyses, the included number of responders is indicated in Table 4. Three separate regression analyses were conducted, and gender, family history of asthma, smoking, occupational exposure to VGDF, living in rural area in childhood, living on a farm in childhood, BMI, age at asthma diagnosis, exercise per week, allergic rhinitis, age, and co-existing COPD were included in the model. Significant risk factors for attacks of breathlessness in the last 12 months in physician-diagnosed asthma were female gender, family history of asthma, adult-diagnosed asthma, and

allergic rhinitis. In child-diagnosed asthma, the risk factors were family history of asthma and allergic rhinitis and in adult-diagnosed asthma, co-existing COPD.

To test if the result differs when co-existing COPD is excluded, we performed sensitivity analyses where the significant variables remained similar (Supplementary Table 3). Similar regression analysis in current asthma is reported in Supplementary Table 5.

DISCUSSION

Adults with asthma diagnosed at adult age were more often symptomatic and had multiple asthma symptoms compared to adults with asthma diagnosed in childhood in this population-based study, even though they used asthma medication more frequently. The greatest risk factor for being symptomatic was diagnosis of asthma in adult age.

Asthma beginning in childhood is usually associated with good treatment response and prognosis, whereas asthma beginning in adulthood is more often a chronic disease.[6,10,11,13,24] We examined asthma symptom prevalence in adults ever being diagnosed with asthma by a physician. Our hypothesis was that adults with adult-diagnosed asthma would be more symptomatic than adults with child-diagnosed asthma. Our results confirmed this hypothesis. The results
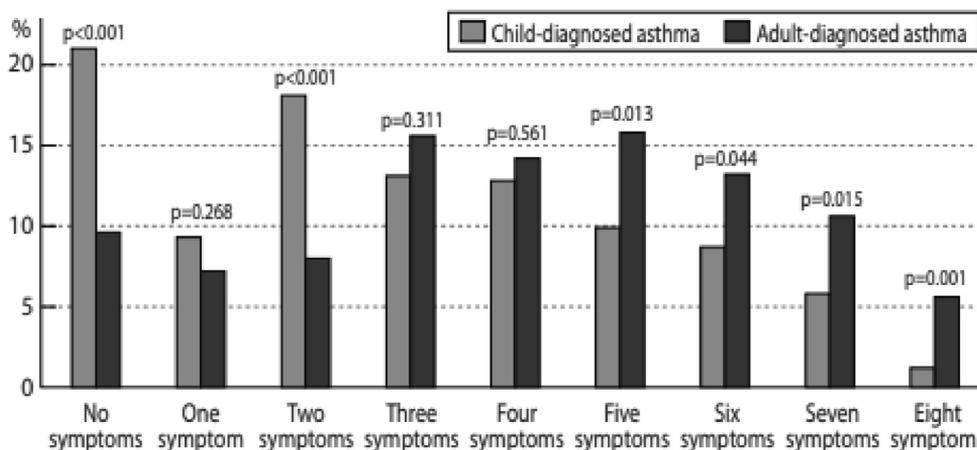
Fig. 1 The burden of asthma symptoms in responders with child- and adult-diagnosed asthma separately as the proportion of responders (%) having zero to eight from the following asthma symptoms: wheeze, longstanding cough, sputum production, dyspnea in cold, dyspnea in exercise, dyspnea mMRC≥2, morning dyspnea and attacks of breathlessness. *P*-values are given above the columns, respectively

| | Child-diagnosed asthma N = 343 | | | | | Adult-diagnosed asthma N = 499 | | | | | | | |
| | Male N = 183 | | Female N = 160 | | P[a] | Male N = 186 | | Female N = 313 | | P[a] | P[b] | P[c] |
	N	%	N	%		N	%	N	%			
Wheeze	80	43.7	78	48.8	0.42	121	65.1	173	55.3	**0.036**	**<0.001**	**0.039**
Longstanding cough	41	22.4	47	29.4	0.14	74	39.8	135	43.1	0.44	**<0.001**	**0.016**
Sputum production	38	20.8	37	23.1	0.57	73	39.2	109	34.8	0.23	**0.010**	0.156
Asthmatic wheeze	39	21.3	43	26.9	0.26	61	32.8	84	26.8	0.18	**0.021**	0.433
Dyspnea in cold	69	37.7	83	51.9	**0.009**	90	48.4	195	62.3	**0.003**	0.196	**0.014**
Dyspnea in exercise	76	41.5	86	53.8	**0.023**	101	54.3	181	57.8	0.47	0.136	0.299
Dyspnea mMRC≥2	19	10.4	33	20.6	**0.002**	55	29.6	121	38.7	0.085	**0.026**	0.261
Morning dyspnea	57	31.1	62	38.8	0.16	80	43.0	143	45.7	0.49	**0.017**	0.057
Attacks of breathlessness	86	47.0	97	60.6	**0.015**	134	72.0	235	75.1	0.53	**<0.001**	**0.004**

Table 3. Gender-specific asthma symptoms and statistical comparison of asthma symptoms in child-diagnosed and adult-diagnosed asthma by gender. [a]*Statistical comparison between males and females by age at asthma diagnosis with chi-square test, adjusted by age.* [b]*Statistical comparison in males and.* [c]*females by age at asthma diagnosis with chi-square test, adjusted by age. Bolded text indicates a statistically significant P-value (P < 0.05)*

remained similar when co-existing COPD was excluded. In adjusted sensitivity analysis conducted with current asthma, the results on asthmatic wheeze and some dyspnea symptoms disappeared but remained on longstanding cough and attacks of breathlessness. This indicates that asthmatics with adult-diagnosis being more symptomatic is not totally explained by asthmatics with child-diagnosis being in remission, that is, symptomless, more often.

Lung function has often been the primary endpoint in clinical studies reflecting asthma control;[4,7,25] whereas the difference in asthma symptoms is less studied, especially in study settings considering age at asthma diagnosis or in the population level.[3,4,7,19] The goal of asthma treatment is to gain good asthma control,[26] meaning symptom control and prevention of disease progression. Therefore, our results are of relevance in the everyday clinic. Furthermore, asthma symptoms and different inflammation markers of asthma are shown to be in concordance,[17] suggesting that assessment of symptoms would be valid to be used as a proxy for the activity of the underlying pathological process.

Many previous studies comparing asthma by age at diagnosis have found little and controversial differences in symptoms between child- and adult-onset asthma.[3,4,19,21] However, some studies have indicated that adult-onset asthma would be less controlled[7,15] in parallel to our finding that multiple symptoms were significantly more prevalent in ever and current adult-diagnosed than child-diagnosed asthma. The controversy probably results from differences in study design–data source, asthma definition, and inclusion criteria. We studied primarily ever, not current asthma.

Gender differences in asthma symptoms are well-established in asthma.[23,27] In our study, adult females with child-diagnosed asthma reported asthma symptoms more frequently than males, which probably results somewhat from higher remission rate in males with child-diagnosed asthma in our data. In adult-diagnosed asthma, there seemed to be difference in reported symptoms; in females, dyspnea in cold and in males, wheezing, was significantly more prevalent than in the other gender, possibly indicating different pathophysiology on average between genders. Similar analysis has not been published by far to the best of our knowledge.

In the present study, the greatest independent risk factor for current attacks of breathlessness was adult-diagnosed asthma. Obesity did not increase this risk significantly. Regular physical exercise has previously been reported to improve asthma
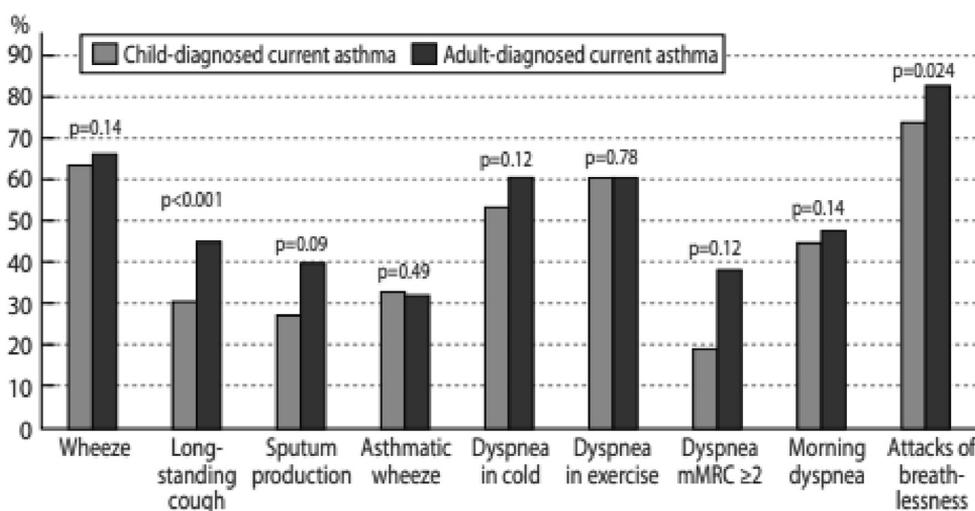
Fig. 2 The prevalence (%) of asthma symptoms in responders with current child- and adult-diagnosed asthma defined by age at asthma diagnosis. Age-adjusted *P*-values are given above the columns, respectively

	All with physician-diagnosed asthma N = 773		Child-diagnosed asthma N = 325		Adult-diagnosed asthma N = 448	
	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P
Female	1.49 (1.07-2.08)	**0.018**	1.62 (0.99-2.66)	0.055	1.40 (0.88-2.25)	0.16
Family history of asthma	1.48 (1.07-2.04)	**0.018**	2.04 (1.23-3.35)	**0.005**	1.16 (0.74-1.81)	0.52
Smoking						
● Never	1		1		1	
● Current	1.17 (0.77-1.78)	0.46	1.19 (0.66-2.15)	0.55	1.13 (0.60-2.13)	0.70
● Ex	0.91 (0.62-1.33)	0.62	0.81 (0.44-1.49)	0.50	0.95 (0.57-1.56)	0.82
Occupational exposure to VGDF	1.25 (0.88-1.77)	0.21	1.24 (0.73-2.11)	0.43	1.18 (0.74-1.89)	0.49
Living in rural area in childhood	1.05 (0.70-1.56)	0.82	0.82 (0.45-1.48)	0.51	1.27 (0.72-2.23)	0.40
Living on a farm in childhood	1.19 (0.75-1.90)	0.46	1.54 (0.70-3.36)	0.28	1.10 (0.60-2.01)	0.77
BMI						
● <24,99	1		1		1	
● 25-29,99	0.94 (0.65-1.37)	0.75	0.81 (0.46-1.44)	0.48	0.96 (0.57-1.59)	0.86
● 30-34,99	1.20 (0.75-1.91)	0.45	1.24 (0.63-2.44)	0.54	1.11 (0.57-2.17)	0.76
● >35	2.07 (0.93-4.59)	0.07	2.71 (0.64-11.51)	0.18	1.73 (0.65-4.60)	0.27
Adult-diagnosed asthma	2.41 (1.64-3.54)	**<0.001**	N/D		N/D	
Exercise <2 times per week	1.25 (0.88-1.79)	0.21	1.13 (0.68-1.88)	0.65	1.54 (0.90-2.61)	0.11
Allergic rhinitis	1.49 (1.07-2.09)	**0.019**	2.25 (1.33-3.79)	**0.002**	1.12 (0.71-1.75)	0.63

Age						
• 60-69	1		1		1	
• 50-59	1.12 (0.66-1.89)	0.67	0.47 (0.14-1.61)	0.23	1.48 (0.80-2.76)	0.22
• 40-49	0.76 (0.45-1.29)	0.31	0.48 (0.15-1.49)	0.20	0.75 (0.39-1.44)	0.39
• 30-39	0.76 (0.45-1.29)	0.31	0.50 (0.17-1.45)	0.20	0.71 (0.36-1.39)	0.32
• 20-29	1.30 (0.73-2.32)	0.37	0.75 (0.26-2.15)	0.60	2.13 (0.65-7.00)	0.21
Co-existing COPD	2.02 (1.0-4.08)	0.052	1.15 (0.23-5.83)	0.87	2.37 (1.05-5.35)	**0.038**

Table 4. Risk factors of attacks of breathlessness in the past 12 months in binary multivariable logistic regression in responders ever been diagnosed with asthma by a physician and in its subcategories, child-diagnosed and adult-diagnosed asthma. *Three different regression analyses were conducted. All the reported variables were included in the model simultaneously. Bolded text indicates a statistically significant P-value (P < 0.05)*

control.[28,29] The present results were in line with this as for current adult-diagnosed asthmatics exercising less than 2–3 times a week was a risk factor for attacks of breathlessness. Smoking did not increase the risk of having asthma symptoms in asthmatic responders in the present study, some-what in contrary to previous results,[4] in which COPD was suggested to explain some of the results. However, we did not have data on pack-years. Nevertheless, adult-diagnosed asthmatics were more symptomatic than child-diagnosed even when co-existing COPD was excluded in this study.

Associative factors with attacks of breathless-ness in adult-diagnosed and child-diagnosed asthma were distinct. Allergic diseases have been recognized as a risk factor for poor asthma control in child-diagnosed asthma[15,21] which is in line with our findings as family history of asthma and allergic rhinitis were associated with attacks of breathlessness in child-diagnosed asthma, whereas the only risk factor in adult-diagnosed asthma for attacks of breathlessness was co-existing COPD.

Responders with adult-diagnosed asthma had more asthma symptoms than those with child-diagnosed asthma in our study. In previous Nordic studies, multi-symptom asthma, defined as physician-diagnosed asthma, asthma medication use, and having multiple asthma symptoms,[16] reflected more severe or uncontrolled disease. Furthermore, uncontrolled asthmatics were prone to exacerbations, and 2% of the Swedish primary health care asthma population, characterized by higher age, were seen to have frequent exacerbations.[30] Therefore, based on the results in the present and past studies, adult-diagnosis would reflect a risk for multi-symptom disease and more severe asthma. Previous studies have suggested obesity and smoking to be associated with an uncontrolled disease in adult-onset asthma and these potential risk factors for being symp-tomatic need an active assessment in patients with adult-onset asthma, to ensure good asthma control.[11]

One could question if there is a difference in patients' education or socioeconomic status at the time of the diagnosis if asthma is diagnosed in childhood compared to a diagnosis in adulthood,

which could potentially lead to differences in medication adherence and a difference in asthma symptom burden. Another Finnish study of adult-onset asthma reported that patients mainly followed in secondary care had poorer adherence to inhalation steroids whereas patients followed in primary health care were adherent to the treatment.[31] As most asthma patients are followed in primary care in Finland the results seen in our study seem unlikely to depend on poorer adherence in responders with adult-diagnosed asthma. Unfortunately, we did not have adherence data in our study.

Living in a rural area or on a farm in childhood was more common among asthmatics diagnosed in adulthood. Another recent paper from the same study cohort reported that childhood exposure to a farming environment did not increase the odds for having asthma. However, it did increase the odds for having asthma diagnosed at late age (defined as age >40).[32]

It has been speculated if adult-onset asthma would be a relapse rather than initiation of the disease and whether asthma symptoms beginning in adulthood would have originated in childhood.[33,34] However, subjects with adult-onset versus child-onset asthma seem to have different basic characteristics, such as gender and BMI,[2,14] which challenges this assumption. In addition, we are beginning to understand the genetic differences between child- and adult-diagnosed asthma due to recent data[5] suggesting that there indeed is a difference in pathophysiology between these age at diagnosis defined groups. These findings show that genetic risk loci are partly similar in both asthma groups but with smaller effects in adult-onset asthma where non-genetic factors may play a more important role.[2]

A substantial part of asthma-related costs for society is caused by sickness absence, and work disability. The risk for work disability correlates with asthma diagnosis age; the later in life asthma is diagnosed, the greater the risk for work disability.[35] Having asthma has been reported to increase the risk of sickness absence markedly in Finland, and having asthma symptoms increased the risk even further.[36,37] Our results are in line with these findings, as responders with adult-diagnosed asthma were more symptomatic. In the present study, the expenses to asthma medication were almost 4-fold in adult-diagnosed compared to child-diagnosed asthmatics. These findings underline the importance of targeting treatment and control visits for this symptomatic patient group of adult-diagnosed asthma both in specialist care and in primary health care to avoid both individual and communal socioeconomic problems and inequality.

The present study has several strengths. We had a large, age comprehensive general population sample. The study sample includes responders both from the city area (Helsinki) and from the countryside (Western Finland). The FinEsS-study has been started already in 1996, and the questionnaire is empirically validated. We had a relatively good response rate considering the decline in response rates during the last decades, and we have previously discussed the matter that the response rate should not affect the results markedly.[14] Therefore, we believe that the current results are well generalizable to the general population. In addition, we asked for physician-diagnosed asthma and age at diagnosis. Considering that asthma diagnoses are based on objective lung function measurements due to the drug reimbursement system in Finland, diagnoses of asthma in this questionnaire-based study are considered reliable.[38]

This study is cross-sectional and therefore descriptive by manner. Recall bias is the main consideration regarding weaknesses in study methods. However, in an earlier study, the age of asthma onset with moderate recall periods was found to be precise, although insensitively centered on mild asthma.[39] Mislabeling of symptoms of other disorders as asthma symptoms and the other way around is also a concern, which is presumably a common problem interplaying between research and clinical practice.[40] Cohort effect is also a matter to consider since the study was cross-sectional and asthma diagnoses retrospective. These considerations could have modified the study result, but we believe that not in a critical amount considering the main results.

In conclusion, asthma diagnosed at adult age is associated with abundant and multiform individual symptoms. Being a common disease, asthma is encountered in the general primary health care population daily. Therefore, recognizing patient

groups with adult-diagnosis and those who would or would not benefit from asthma controls and specialist care is crucial both for resource optimization and for gaining comprehensively better asthma control.

Availability of data and materials
The datasets used and analysed in this current study are available from the corresponding author on reasonable request.

Authors' contributions
HH-M, JH, PPi, PPa, PI and HK designed the study and wrote the report. JH and HH-M performed the statistical analyses with help from PI and PPi. PPi, PPa, AL, AS and HH-M contributed to the FinEsS Helsinki sample, population sample and questionnaires. HK, PI, HA and LT contributed to the FinEsS Western sample. All authors contributed to interpretation of the data and made critical revisions of the manuscript. All authors read and approved the final version of the publication and gave consent to publication.

Ethics approval
The study was approved by the Coordinating Ethics Committee of Helsinki and Uusimaa Hospital District (200/13/03/00/2015).

Potential competing interests
Päivi Piirilä reports financial support from NordForsk Foundation. Leena Tuomisto reports payments for lectures from GlaxoSmithKline, AstraZeneca and Boehringer Ingelheim. Helena Backman reports payments for scientific presentations from AstraZeneca and Boehringer Ingelheim. Hannu Kankaanranta reports personal fees from AstraZeneca, Boehringer Ingelheim, Chiesi Pharma AB, GlaxoSmithKline, MSD, Orion Pharma, Novartis, Sanofi Genzyme and fees for lectures from AstraZeneca, Orion Pharma and Mundipharma. Lauri Lehtimäki reports payments for lectures from AstraZeneca, Boehringer Ingelheim, Chiesi, Circassia, GSK, Mundipharma, Novartis, Sanofi, Orion Pharma and additionally Advisory Boards participation for Alk, AstraZeneca, Boehringer Ingelheim, Chiesi, GSK, Novartis, Sanofi, OrionPharma. LL reports owning stocks of Ausculthing Oy and being PI in clinical trials/studies sponsored by OrionPharma. Pinja Ilmarinen reports lecture fees from GlaxoSmithKline, Novartis, Mundipharma and AstraZeneca. Pinja Ilmarinen is an employee of GlaxoSmithKline. Hanna Hisinger-Mölkänen has been an employee of GlaxoSmithKline and is an employee of Orion Pharma. The other authors have no competing interests.

Appendix A. Supplementary data
Supplementary data to this article can be found online at https://doi.org/10.1016/j.waojou.2022.100675.

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PUBLICATION
IV

Nonrespiratory diseases in adults without and with asthma by age at asthma diagnosis

Honkamäki J, Ilmarinen P, Hisinger-Mölkänen H, Tuomisto LE, Andersén H, Huhtala H, Sovijärvi A, Lindqvist A, Backman H, Nwaru BI, Rönmark E, Lehtimäki L, Pallasaho P, Piirilä P, Kankaanranta H

Original Article

Nonrespiratory Diseases in Adults Without and With Asthma by Age at Asthma Diagnosis

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What is already known about this topic? Asthma seems to differ by age of onset in many ways. Subjects with asthma have also been previously found to suffer from more nonrespiratory common chronic diseases than subjects without asthma.

What does this article add to our knowledge? This study finds that with older age at asthma diagnosis, the number of nonrespiratory diseases associated with asthma increase. In addition, the asthma-associated nonrespiratory diseases are different by age at asthma diagnosis.

How does this study impact current management guidelines? Multimorbidity in asthma diagnosed at older age should be better noticed in clinical practice and scientific studies. Different associations between nonrespiratory diseases and asthma diagnosed at different ages could be explained by common pathogenic processes.

BACKGROUND: Chronic nonrespiratory diseases are seemingly more prevalent in subjects with than without asthma, and asthma seems to differentiate by age of onset. However, studies with comparison of nonrespiratory diseases in subjects with and without asthma, considering asthma age of onset, are scarce.

OBJECTIVE: To compare the quantity and type of chronic nonrespiratory diseases in adults with and without asthma considering age at asthma diagnosis.

METHODS: In 2016, a FinEsS questionnaire was sent to 16,000 20- to 69-year-old adults randomly selected in Helsinki and

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Western Finland populations. Physician-diagnosed asthma
was categorized to early (0-11), intermediate (12-39), and
late-diagnosed (40-69 years).
RESULTS: A total of 8199 (51.5%) responded, and 842 (10.3%)
reported asthma and age at diagnosis. In age and sex-adjusted
binary logistic regression model, the most represented non-
respiratory disease was treated gastroesophageal reflux disease in
early-diagnosed (odds ratio, 1.93; 95% CI, 1.17-3.19; $P = .011$)
and osteoporosis in both intermediate-diagnosed (odds ratio,
3.45; 95% CI, 2.01-5.91; $P < .001$) and late-diagnosed asthma
(odds ratio, 2.91; 95% CI, 1.77-4.79; $P < .001$), compared with
subjects without asthma. In addition, gastroesophageal reflux
disease, depression, sleep apnea, painful condition, and obesity
were significantly more common in intermediate- and late-
diagnosed asthma compared with without asthma, and similarly
anxiety or panic disorder in intermediate-diagnosed and hyper-
tension, severe cardiovascular disease, arrhythmia, and diabetes
in late-diagnosed asthma. In age-adjusted analyses, having 3 or
more nonrespiratory diseases was more common in intermediate
(12.1%) and late-diagnosed asthma (36.2%) versus without
asthma (10.4%) (both $P < .001$).
CONCLUSIONS: Nonrespiratory diseases were more common
in adults with asthma than in adults without asthma. The type of
nonrespiratory diseases differed, and their frequency increased
by increasing age at asthma diagnosis.   © 2022 The Authors.
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INTRODUCTION

During the past decade, asthma heterogeneity has become well
recognized, and phenotyping and endotyping of asthma have had
promising results in dealing with it.[1] Age of asthma onset has
been identified as an important influencer of asthma pheno-
types[1,2]; however, phenotyping studies have rarely considered
asthma comorbidities.

The burden of comorbidities especially in adult patients with
asthma is marked: more than 50% suffer from a nonrespiratory
comorbid condition.[3,4] In addition, comorbidities most probably
act as confounding factors in asthma studies.[5] Better identifica-
tion of comorbidities related to asthma could also play an
important role in unraveling molecular mechanisms especially in
less understood adult-onset asthma[2]— indeed, a recent review[6]
summarized several shared mechanisms between asthma and
other common chronic diseases.

In recent register and population samples, some non-
respiratory comorbidities are suggested to be more prevalent in
subjects suffering from asthma.[7-10] Evidence of this coexistence
has been published at least on dyspepsia,[8,9] cardiovascular dis-
eases,[11-13] obesity,[10,14] mental disorders,[15] depression,[6,8,10]
osteoporosis,[8] diabetes,[8] and sleep apnea.[16] Nevertheless, evi-
dence is limited to few or no studies regarding some common
chronic diseases and their relationship with asthma.[17]

Furthermore, although age of asthma onset is a key modifier
of asthma,[1,2,18,19] few studies have investigated the influence of
age of asthma onset on coexistence of nonrespiratory diseases in
patients with asthma, or simultaneously made comparisons be-
tween subjects with and without asthma. In the few studies, age
of asthma onset is also limited to dichotomous categorization to
childhood- and adult-onset asthma,[11,13,20,21] although more
differences are presumed to be found if adult-onset asthma is
further divided into earlier and later adult-onset asthma.[18,22,23]

Therefore, we aimed to investigate nonrespiratory diseases in
subjects with and without asthma, considering age at asthma
diagnosis. We hypothesized that subjects with asthma would
suffer more often from nonrespiratory diseases than subjects
without asthma, and that increasing age at asthma diagnosis
would increase the quantity of the nonrespiratory diseases
coexistent with asthma.

METHODS

Study subjects

In 2016, a FinEsS questionnaire was sent to 16,000 subjects aged
20 to 69 years. Subjects were randomly selected by Statistics Finland
from Helsinki and Western Finland areas conforming the age and
sex distribution in the population. Power analyses were made to
define the sufficient study size, and an approval of the Ethics
Committee of Helsinki University Hospital was received before the
initiation of the study.

Study design

Detailed description of the study methods and the FinEsS
questionnaire is reported elsewhere.[24,25]

The common variables were defined as follows.

Physician-diagnosed asthma by a positive and *without asthma* by a
negative answer to "Have you been diagnosed by a doctor as having
asthma?"

Age at asthma diagnosis "What age were you when asthma was
diagnosed?"

Age at asthma diagnosis in those aged 0 to 11 years was defined as
early-diagnosed, 12 to 39 years as *intermediate-diagnosed*, and 40 to
69 years as *late-diagnosed asthma.* The cutoff points were chosen on
the basis of asthma incidence shifts.[19,21] Age 12 years is also most
often used to delineate child- and adult-onset asthma,[23] and age 40
years suggested to be a cutoff point needing more research.[19,22]

COPD "Have you been diagnosed by a physician as having
chronic bronchitis, chronic obstructive pulmonary disease (COPD),
or emphysema?"

Allergic rhinitis "Have you been diagnosed by a doctor as having
allergic rhinitis caused by pollen?" or "Have you been diagnosed by a
doctor as having other allergic rhinitis?"

Obesity Self-reported body mass index (BMI) greater than or
equal to 30.

Other nonrespiratory diseases with the question "Has a physician
diagnosed you with any of the following diseases" and an affirmative
positive answer to following:

Coronary artery disease "Coronary disease."

Heart failure "Heart insufficiency."

Stroke or TIA "Cerebral infarction or TIA (transient ischemic attack)."

Hypertension "Hypertension."

Arrhythmia "Atrial fibrillation or other arrhythmia."

Depression "Depression."

Anxiety or panic disorder "Panic disorder or anxiety disorder."

Gastroesophageal reflux disease (GERD) "Treatment or medication to esophageal reflux disease (dyspepsia or GERD)."

Sleep apnea "Sleep apnea."

Diabetes "Diabetes."

Chronic kidney failure "Chronic renal insufficiency."

Osteoporosis "Osteoporosis."

Painful condition "Pain, that requires daily usage of pain killers."

Severe cardiovascular disease "Heart failure," "Coronary disease," or "Stroke or TIA."

Number of nonrespiratory diseases included the following 14 diseases: hypertension, arrhythmia, heart failure, coronary artery disease, stroke or TIA, depression, anxiety or panic disorder, diabetes, GERD, chronic kidney failure, sleep apnea, osteoporosis, painful condition, and obesity.

Asthma medication use "Do you currently use asthma medication (permanently or as needed)?"

Statistical analyses

Analyses were conducted with SPSS Statistics version 26 (IBM). Associations between categorical variables were analyzed by χ^2 or Fisher exact test. Associations between dichotomous categorical and normally distributed continuous variables were analyzed by t test, and nonnormally distributed continuous variables by Mann-Whitney test. In case of 3 or more strata to compare, 1-way ANOVA for normally distributed and Kruskal-Wallis test for nonnormally distributed continuous variables were used. Normality was assessed by Kolmogorov-Smirnov analysis.

Both multivariable and univariate binary logistic regression analyses were used to estimate odds ratios (ORs). The outcome variables in the analyses were nonrespiratory diseases. The covariates were chosen by clinical experience of the most important confounding factors before the analyses, and age and sex were used in all the analyses as covariates. Sensitivity analyses were conducted by excluding COPD and including more covariates, smoking, COPD, and BMI, to the regression models. Age was used as a continuous variable and other covariates as categorical. A P value of less than .05 was considered statistically significant, and CIs with 95% accuracy were reported. Bonferroni correction was applied to 3 strata comparisons in categorical variables, for which the corresponding level of statistical significance was less than .017. Subjects lacking full smoking data were excluded from the analyses.

RESULTS

Basic characteristics of the study subjects and nonresponders

Altogether, 8199 (51.5%) responded. Detailed demographic characteristics of the responders are published elsewhere.[23-25] Briefly, median age of the responders was 50 years, and males consisted a minority (44.9%) of the responders, whereas median age of the nonresponders was 36 years in Helsinki and 40 years in Western Finland data, and the nonresponders were more often males (53.1%).

Physician-diagnosed asthma was reported by 879, and age at asthma diagnosis by 842 subjects: early-diagnosed asthma by 245 (29.1%), intermediate-diagnosed by 358 (42.5%), and late-diagnosed by 239 (28.4%) subjects. In total, 7051 subjects did not have asthma. BMI was highest and current smoking the least prevalent in late-diagnosed asthma, whereas allergic rhinitis and family history of asthma the most common in early-diagnosed asthma (Table I).

Different nonrespiratory diseases

The most common diseases were hypertension in subjects without asthma (18.9%) and with late-diagnosed asthma (42.3%), and obesity in early- (17.5%) and intermediate-diagnosed asthma (21.1%) (Table II). Prevalence of some of the most common studied diseases in subjects 40 years or older is illustrated in Figure 1. In addition, demographic characteristics and nonrespiratory diseases in subjects 40 years or older are reported in Table E1 in this article's Online Repository at www.jaci-inpractice.org.

In subjects with physician-diagnosed asthma versus without asthma, the median age was lower (47 vs 50 years; $P = .006$), but most of the analyzed diseases were significantly more prevalent in those with physician-diagnosed asthma (see Table E2 in this article's Online Repository at www.jaci-inpractice.org). When subjects with COPD were excluded, most of the statistically significant differences remained (see Table E3 in this article's Online Repository at www.jaci-inpractice.org).

Number of nonrespiratory diseases

One or more nonrespiratory diseases were reported by 3260 (47.0%) subjects without asthma and 508 (58.7%) subjects with physician-diagnosed asthma ($P < .001$). Number of nonrespiratory diseases more than 1 was significantly higher in all age groups at asthma diagnosis strata compared with without asthma, and highest in late-diagnosed asthma compared with early- and intermediate-diagnosed asthma.

The number of nonrespiratory diseases is visualized in Figure 2. In both all and subjects 40 years or older, 3 and 4 diseases and 5 or more diseases, respectively, were most commonly present in subjects with late-diagnosed asthma.

Nonrespiratory diseases in multivariable logistic regression model

To compare the risk of individual diseases between subjects with and without asthma by age at asthma diagnosis, we conducted multivariable binary logistic regression analysis. In age- and sex-adjusted analysis, the variables significantly more common in subjects with asthma despite of diagnosis age compared with without asthma were GERD, COPD, and 1 or more nonrespiratory disease (Table III). The most overrepresented disease in subjects with physician-diagnosed asthma compared with those without asthma was GERD in early-diagnosed (OR, 1.93; 1.17-3.19; $P = .011$) and osteoporosis in both intermediate-diagnosed (OR, 3.45; 2.01-5.91; $P < .001$) and late-diagnosed asthma (OR, 2.91; 1.77-4.79; $P < .001$). The univariate analyses can be found in Table E4 in this article's Online Repository at www.jaci-inpractice.org.

Interestingly, as COPD was excluded, intermediate-diagnosed asthma became a significant risk factor of stroke or TIA (OR, 2.33; 1.15-4.71; $P = .019$) and late-diagnosed asthma lost significant association with severe cardiovascular disease (see

TABLE I. Demographic characteristics of subjects without and with asthma by age at asthma diagnosis strata

Variable	Without asthma (N = 7051)		Early-diagnosed asthma (0-11 y; N = 245)		Intermediate-diagnosed asthma (12-39 y; N = 358)		Late-diagnosed asthma (40-69 y; N = 239)	
	Median	Q₁-Q₃	Median	Q₁-Q₃	Median	Q₁-Q₃	Median	Q₁-Q₃
Age (y)	50	35-61	32	26-44	42	32-54	62	57-66
Years since diagnosis	ND	ND	27	20-39	19	10-28	10	4-17
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
BMI*	26.0	6.4	25.6	4.8	26.5	5.2	28.1	5.4
	N	%	N	%	N	%	N	%
Sex: female	3855	54.7	98	40.0	223	62.3	152	63.6
Allergic rhinitis	1275	18.1	174	71.0	228	63.7	85	35.6
Family history of asthma	1523	21.6	112	45.7	159	44.4	104	43.5
Smoking								
Never	3838	54.4	124	50.6	172	48.0	98	41.0
Current	1508	21.4	68	27.8	80	22.3	49	20.5
Ex	1705	24.2	53	21.6	106	29.6	92	38.5
Asthma medication use	282	4.0	148	60.4	256	71.5	212	88.7

ND, Not defined; *Q₁-Q₃*, quartiles.
*Missing =126.

TABLE II. Nonrespiratory diseases and COPD in subjects without and with asthma by age at asthma diagnosis strata and statistical comparison between age at asthma diagnosis strata adjusted by age and sex

Variable	Without asthma (N = 7051)		Early-diagnosed asthma (0-11 y; N = 245)		Intermediate-diagnosed asthma (12-39 y; N = 358)		Late-diagnosed asthma (40-69 y; N = 239)		P
	N	%	N	%	N	%	N	%	
Hypertension	1333	18.9	27	11.0	58	16.2	101	42.3	.23
Severe cardiovascular disease	344	4.9	6	2.4	11	3.1	30	12.6	.65
Coronary artery disease	165	2.3	1	0.4	1	0.3	15	6.3	.14
Arrhythmia	419	5.9	11	4.5	21	5.9	38	15.9	.65
Heart failure	87	1.2	1	0.4	2	0.6	8	3.3	.56
Stroke or TIA	140	2.0	4	1.6	9	2.5	14	5.9	.87
Diabetes	404	5.7	6	2.4	18	5.0	35	14.6	.30
Depression	733	10.4	29	11.8	59	16.5	42	17.6	.38
Anxiety or panic disorder	427	6.1	17	6.9	43	12.0	18	7.5	.04
GERD	399	5.7	18	7.3	37	10.3	44	18.4	.92
Chronic kidney failure	51	0.7	1	0.4	3	0.8	3	1.3	.79
Sleep apnea	247	3.5	7	2.9	19	5.3	26	10.9	.32
Osteoporosis	122	1.7	1	0.4	17	4.7	21	8.8	.22
Painful condition	460	6.5	12	4.9	36	10.1	51	21.3	.31
Obesity*	1152	16.6	42	17.5	75	21.1	73	31.1	.34
COPD	97	1.4	8	3.3	28	7.8	44	18.4	.05

P < .017 was the threshold for statistical significance due to Bonferroni correction for multiple comparisons.
*Missing = 126.

Table E5 in this article's Online Repository at www.jaci-inpractice.org).

When regression analysis was adjusted by COPD, smoking, and BMI in addition to age and sex, we saw hypertension, severe cardiovascular disease, and diabetes lose their significant associations with late-diagnosed asthma compared with without asthma. Otherwise, significant associations remained similar (Table IV). To point out, after these adjustments, sleep apnea and depression remained significant in both intermediate- and late-diagnosed asthma as opposed to without asthma.

DISCUSSION

In this population-based study, we found that adults with asthma suffer from nonrespiratory diseases and multimorbidity more often than adults without asthma. In adjusted analyses, the number of nonrespiratory diseases was greater at older age at asthma diagnosis than when asthma was diagnosed at younger ages.

Some associations between asthma and nonrespiratory diseases have been previously described.[7-10] However, different age of asthma onset has been considered only in a few previous studies
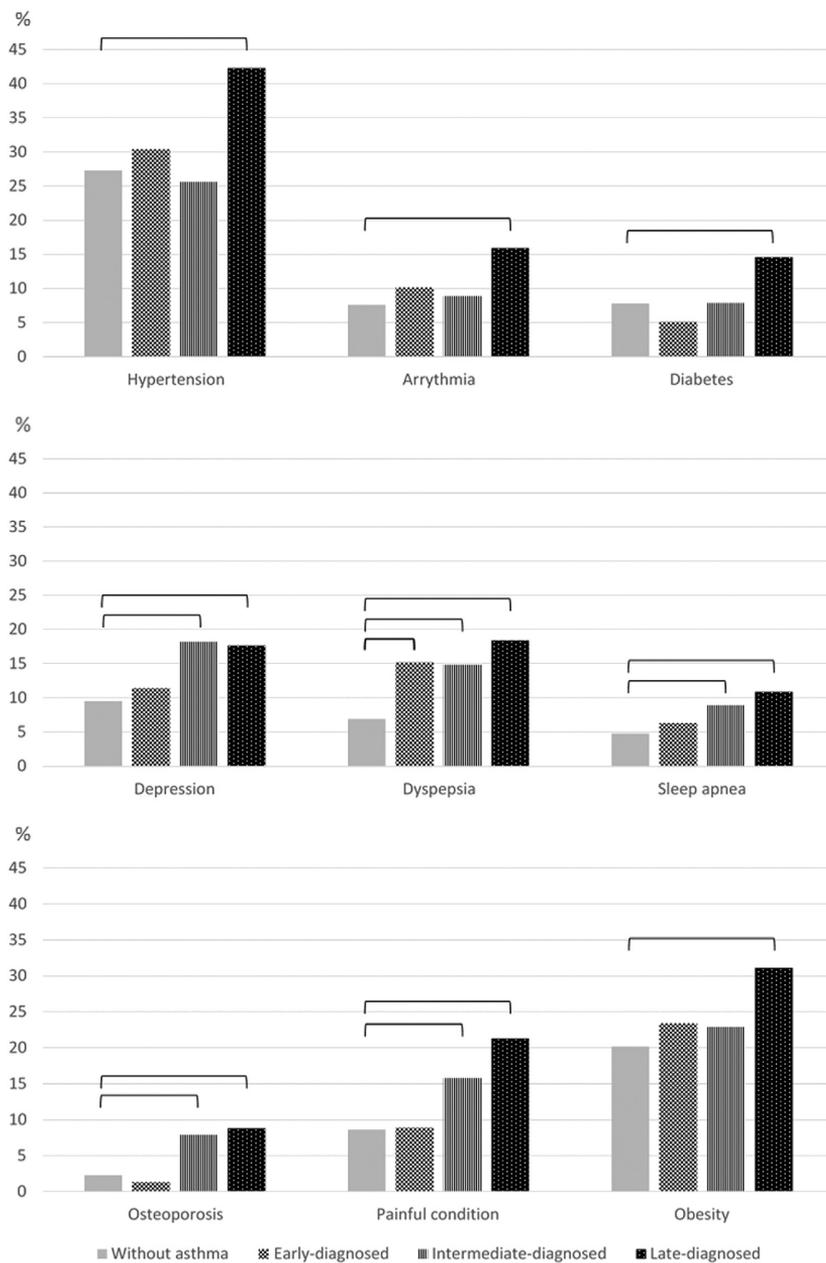
FIGURE 1. Prevalence (%) of different nonrespiratory diseases in subjects with and without asthma by age at asthma diagnosis. Only subjects 40 years or older are included. *P* less than .05 between without asthma and different asthma strata are marked with connector lines. Analyses were done with logistic regression and adjusted by age and sex.

investigating asthma and its nonrespiratory comorbidities[11,13,20,21] but otherwise than in this study, they have usually not included controls without asthma,[11,20,21] analyses have been concentrated to a limited group of diseases,[11,13,15,21] or study subjects have represented only, for example, severe asthma and not asthma in the general population.[20,21] Neither have they categorized asthma to more than 2 strata by age of onset,[11,13,15,21] although more age of onset strata would be
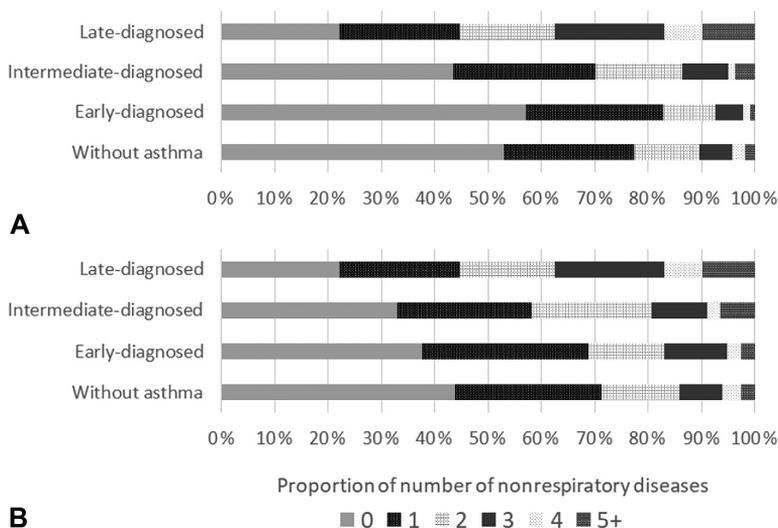
FIGURE 2. Number of nonrespiratory diseases in subjects with and without asthma by age at asthma diagnosis in (**A**) all subjects and (**B**) subjects 40 years or older.

TABLE III. The risk of nonrespiratory diseases and COPD in subjects with early-, intermediate-, and late-diagnosed asthma vs subjects without asthma in multivariable binary logistic regression analysis adjusted by age and sex

Variable	Early-diagnosed asthma (0-11 y)		Intermediate-diagnosed asthma (12-39 y)		Late-diagnosed asthma (40-69 y)	
	OR (95 % CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*
Hypertension	1.49 (0.94-2.37)	.09	1.31 (0.95-1.80)	.10	1.54 (1.17-2.03)	**.002**
Severe cardiovascular disease	1.07 (0.46-2.51)	.88	1.00 (0.54-1.88)	.99	1.61 (1.07-2.41)	**.02**
Arrhythmia	1.29 (0.69-2.43)	.42	1.29 (0.81-2.04)	.28	1.94 (1.34-2.79)	**<.001**
Stroke or TIA	1.9 (0.69-5.42)	.21	1.92 (0.95-3.86)	.068	1.75 (0.99-3.11)	.06
Diabetes	0.76 (0.33-1.75)	.52	1.25 (0.76-2.10)	.38	1.75 (1.19-2.56)	**.004**
Depression	1.13 (0.76-1.69)	.55	1.60 (1.20-2.14)	**.002**	2.00 (1.41-2.84)	**<.001**
Anxiety or panic disorder	1.09 (0.65-1.81)	.75	1.96 (1.40-2.74)	**<.001**	1.43 (0.87-2.37)	.16
GERD	1.93 (1.17-3.19)	**.011**	2.17 (1.52-3.12)	**<.001**	2.77 (1.95-3.93)	**<.001**
Sleep apnea	1.17 (0.53-2.56)	.70	2.38 (1.45-3.91)	**.001**	2.57 (1.65-4.00)	**<.001**
Osteoporosis	0.63 (0.086-4.60)	.65	3.45 (2.01-5.91)	**<.001**	2.91 (1.77-4.79)	**<.001**
Painful condition	1.28 (0.70-2.33)	.43	1.91 (1.33-2.75)	**.001**	2.54 (1.83-3.54)	**<.001**
Obesity	1.41 (1.0-2.0)	.051	1.52 (1.16-1.98)	**.002**	1.72 (1.29-2.30)	**<.001**
COPD	4.38 (1.03-9.43)	**<.001**	8.40 (5.33-13.22)	**<.001**	10.74 (7.20-16.01)	**<.001**
No. of nonrespiratory diseases ≥1	1.48 (1.13-1.95)	**.005**	1.88 (1.50-2.36)	**<.001**	2.27 (1.65-3.12)	**<.001**
No. of nonrespiratory diseases ≥2	1.30 (0.91-1.86)	.16	1.94 (1.52-2.49)	**<.001**	2.59 (1.98-3.40)	**<.001**
No. of nonrespiratory diseases ≥3	1.36 (0.82-2.27)	.23	1.86 (1.34-2.59)	**<.001**	3.14 (2.36-4.17)	**<.001**

Without asthma was coded as 0 and in each regression analysis, diagnosis-age stratum as 1. Bolded text indicates statistical significance (*P* < .05).

justified.[19,22,23] Therefore, only very limited information exists previously on the association between asthma categorized by age of onset and other chronic nonrespiratory diseases.

We found several nonrespiratory diseases to be more common not in early-diagnosed but in intermediate- and late-diagnosed asthma compared with subjects without asthma in age- and

TABLE IV. The risk of nonrespiratory diseases in subjects with early-, intermediate-, and late-diagnosed asthma vs subjects without asthma in multivariable binary logistic regression analysis adjusted by age, sex, COPD, smoking, and BMI

Variable	Early-diagnosed asthma (0-11 y)		Intermediate-diagnosed asthma (12-39 y)		Late-diagnosed asthma (40-69 y)	
	OR (95 % CI)	P	OR (95% CI)	P	OR (95% CI)	P
Hypertension	1.37 (0.84-2.23)	.20	1.12 (0.80-1.58)	.51	1.30 (0.96-1.75)	.09
Severe cardiovascular disease	1.02 (0.43-2.41)	.97	0.91 (0.48-1.71)	.76	1.28 (0.83-1.98)	.26
Arrhythmia	1.27 (0.67-2.39)	.47	1.09 (0.68-1.76)	.72	1.64 (1.11-2.41)	**.01**
Stroke or TIA	1.81 (0.64-5.12)	.27	1.74 (0.85-3.55)	.13	1.43 (0.78-2.64)	.25
Diabetes	0.73 (0.31-1.70)	.46	1.05 (0.63-1.75)	.85	1.41 (0.94-2.11)	.10
Depression	1.00 (0.66-1.53)	.98	1.45 (1.08-1.95)	**.015**	1.74 (1.20-2.52)	**.003**
Anxiety or panic disorder	1.01 (0.59-1.71)	.98	1.85 (1.31-2.61)	**<.001**	1.32 (0.78-2.21)	.30
GERD	1.95 (1.18-3.24)	**.009**	2.14 (1.48-3.08)	**<.001**	2.80 (1.94-4.03)	**<.001**
Sleep apnea	1.10 (0.50-2.43)	.82	2.06 (1.23-3.43)	**.006**	1.99 (1.23-3.20)	**.005**
Osteoporosis	0.58 (0.078-4.24)	.59	2.97 (1.69-5.22)	**<.001**	2.41 (1.41-4.16)	**.001**
Painful condition	1.23 (0.67-2.27)	.50	1.64 (1.12-2.39)	**.011**	2.05 (1.44-2.92)	**<.001**
No. of nonrespiratory diseases ≥1	1.44 (1.07-1.96)	**.018**	1.63 (1.27-2.10)	**<.001**	1.75 (1.23-2.48)	**.002**
No. of nonrespiratory diseases ≥2	1.22 (0.83-1.80)	.32	1.64 (1.24-2.17)	**<.001**	2.01 (1.48-2.72)	**<.001**
No. of nonrespiratory diseases ≥3	1.28 (0.73-2.23)	.39	1.48 (1.02-2.15)	**.038**	2.52 (1.82-3.49)	**<.001**

Without asthma was coded as 0 and in each regression analysis, diagnosis-age stratum as 1. Bolded text indicates statistical significance ($P < .05$).

sex-adjusted analyses. Additionally adjusting for smoking, BMI, and COPD generally diminished these associations, most of which remained significant. As asthma diagnosis-age strata were compared with each other, none of the analyzed diseases differed between them. Another recent study that included quite a versatile set of chronic diseases neither found any of the analyzed diseases to differ between age of onset—defined difficult asthma.[20] In that study, asthma was divided only to 2 strata by age of onset, and subjects without asthma were not included.

In our results, we demonstrated that not only was asthma associated with more comorbid diseases, as has been reported before,[3] but also that later age at asthma diagnosis was associated with a higher number of nonrespiratory diseases. To our knowledge, this was the first study to describe age-independent association with age at asthma diagnosis and number of nonrespiratory comorbid diseases.

The prevalence of obese responders with asthma increased with age at diagnosis in our study. Obesity is previously found to impact child-onset asthma severity more than adult-onset asthma.[26] However, only adult-onset asthma is found to have a genetic association with obesity,[27] and many studies have found obesity to associate especially with adult-onset female asthma.[1,14,20] Therefore, obesity seems to play a different role in asthma depending on asthma diagnosis age.

GERD is commonly found to associate with asthma,[8,9] but as a novel finding, it also had an increasing association with asthma by increasing asthma diagnosis age in our results. Variable results on proton pump inhibitor treatment influencing asthma outcome are reported.[5] However, long-term acid-suppressive medication has been shown to increase asthma risk.[28]

In our data, depression was more prevalent in subjects with intermediate- or late-diagnosed asthma than in subjects without asthma. Anxiety or panic disorder, however, was more prevalent in those with intermediate-diagnosed asthma than in those without asthma, being a novel finding. Of mental disorders, especially depression has been reported previously to have a significant association with asthma.[8,10] It is linked to asthma in a genetic manner[29] and is also associated with poorer control of asthma[30] and has common molecular pathways with asthma.[6] Common molecular pathways and genetics may explain the association mostly, but also the burden of asthma could play a role in development of depression.

Osteoporosis was associated with intermediate- and late-diagnosed asthma, and it had the most marked association with asthma in these age at diagnosis strata of the analyzed diseases. It was not significantly associated with early-diagnosed asthma. This could indirectly indicate a more difficult disease if asthma is diagnosed in adulthood and by implication, an emphasized corticosteroid use, which predisposes to osteoporosis.[31,32] However, other factors may also have an impact, and indeed, the pathogenetic processes have similarities between osteoporosis and asthma.[31] Corticosteroid use may also play an important role in other associations between asthma and other chronic diseases investigated in this study.

In this study, late-diagnosed asthma was associated with hypertension, cardiac arrhythmia, and severe cardiovascular diseases, but we demonstrated that the associations mostly disappeared after further adjusting for smoking, COPD, and BMI. Of cardiovascular diseases, especially hypertension has been associated with asthma earlier.[8,11,12] Another study

described association of cardiovascular diseases with adult-onset, but not with child-onset, asthma.[11] Consistently with our results, almost all significant associations disappeared as the model was further adjusted with lifestyle-associated variables in that study. Yet another study considering age of onset did not find differences between child- and adult-onset asthma[13] but adult-onset asthma was limited to onset at 54 years of age maximum. Subjects with asthma may suffer from both hypertension and arrhythmias more often due to harmful effects of asthma medication, community in inflammation status or metabolic condition, or even mechanisms related to subjective burden of asthma, stress, or lack of sleep.[6,12]

Subjects with intermediate- and late-diagnosed asthma had more sleep apnea than subjects without asthma in this study. Asthma and sleep apnea have been associated before also.[16] Furthermore, controlling for obese subjects in this study diminished but did not abolish the associations. Thus, our study indicates that other factors than obesity must also play a role in this association.

Subjects with intermediate- and late-diagnosed asthma had more painful condition than those without asthma, with a prominent effect size even after adjusting for lifestyle factors in this study. The etiology of painful condition was not defined and could result from either individual or multifactorial cause. Perhaps of its ambiguity, it is a condition and a variable mainly overlooked in previous studies investigating comorbidities of asthma. Regarding cause of this association, regular paracetamol use has been previously connected with asthma prevalence.[33]

Because COPD is shown to associate with more comorbidities than asthma,[34] and misdiagnoses between asthma and COPD is a frequent concern, we did sensitivity analyses by excluding coexisting COPD. This did not generally change the results markedly. COPD was most common in late-diagnosed asthma compared with other diagnosis-age strata, and it is also one of the few comorbidities previously identified to differ between age of asthma onset phenotypes: it was more common in adult-onset than in child-onset asthma in a recent study that was, however, limited to severe asthma.[20]

Generally, various potential explanations for associations between asthma and nonrespiratory diseases exist. Many of them have common genetic or molecular mechanisms with asthma,[6,14] whereas others share environmental risk factors with asthma.[6] Some diseases are also influenced by asthma medication, such as osteoporosis and diabetes.[6] In addition, genetic differences seem to be associated more with child-onset disease[1,35] and environmental factors with later-onset asthma.[2] They seem also to differ in asthma pathogenesis.[2,17]

Strengths of this study include a large, multicenter general population sample with no marked exclusions, and therefore the result generalizability should finely extend to the general population. We included subjects with a broad age range (20-69 years), which is quite rarely seen in asthma studies. Furthermore, the study is a part of a larger consortium, and the questionnaire and other study procedures have been previously validated empirically, as dozens of original articles have followed since the initial FinEsS study in 1995. Finally, the data are collected from areas in which asthma diagnoses are generally very reliable due to good availability of spirometry and peak expiratory flow, high standard physician and nurse training, and disciplinarily followed, uniform national protocols.[36] There is also a requirement

of objective asthma diagnosis to obtain asthma medication reimbursement in Finland.

The main weaknesses of this study are as follows. Concern of recall bias related to preciseness of asthma diagnosis age is a major consideration. However, it is demonstrated that retrospective assessment of self-reported age at diagnosis of asthma is specific and widely used.[24,37] Furthermore, in Finland, patients with newly diagnosed asthma are granted an asthma medication reimbursement and a new governmental insurance card holding the issue date that corresponds roughly to time at diagnosis, enhancing the memory trace. The reimbursement system and issue card have been used since 1970, covering most of the study period. When assessing reliability of self-report of the diagnoses of diseases, they are found to be relatively reliable, but mostly underreported,[38] which applies also to asthma.[37] However, overdiagnosis of asthma is also common, and diagnosing asthma is particularly challenging.[39] However, in Finland, the common practice is to objectively measure lung function in asthma diagnosis.[36] It is also notable that cohort effect affects the current results because diagnostic tools and practice have changed over time, and asthma diagnoses reflect a long period as the study was cross-sectional asking for asthma diagnosis age.

Furthermore, the study could have been done by using register data, and therefore the validity of presence of the different chronic diseases could have been better. Finally, our response rate of 52% is a level that has been quite common in questionnaire studies recently, which should not deviate the result markedly in asthma studies, as we have discussed previously with detail.[24] In addition, the responders were more often older subjects, in which diseases were also more prevalent.

Comorbidities supposedly confound results of asthma phenotyping studies,[3] and other studies of asthma control. Higher number of comorbidities is previously associated with lower Asthma Control Test score,[4] and obesity and mental diseases have also been found to independently influence asthma control negatively.[6,30,40] The potential of comorbidities acting as confounding factors in many ways is therefore quite significant, which also the current results support—not only age but also age at asthma diagnosis influences diseases associated with asthma. Furthermore, better identification of asthma multimorbidity would benefit by unraveling possibilities in more holistic and personalized treatment approach. In addition, concentration on asthma comorbidities could promote finding common molecular pathways between asthma and other diseases to target future treatment methods and better understanding of pathogenesis especially regarding adult-onset asthma, in which specific mechanisms are mostly unknown, contributing to worse outcomes.[2]

CONCLUSIONS

Adults with asthma suffer overall from many more diseases than adults without asthma. Age at asthma diagnosis modified frequency of diseases, so that the number of nonrespiratory diseases increased by increasing age at asthma diagnosis. The results could indicate not only that higher corticosteroid usage, especially in adult-onset asthma, predisposes to other chronic diseases but also that asthma shares several molecular mechanisms with other chronic diseases. Better understanding of comorbid diseases could help us in obtaining enhanced asthma

control, and for the first thing, they should be more readily noted in studies of adult asthma.

Acknowledgments

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TABLE E1. Demographic characteristics, nonrespiratory diseases, and COPD in subjects without and with asthma by age at asthma diagnosis strata and statistical comparison between age at asthma diagnosis strata adjusted by age and sex in subjects aged ≥40 y

Variable	Without asthma (N = 4699)		Early-diagnosed asthma (N = 79)		Intermediate-diagnosed asthma (N = 203)		Late-diagnosed asthma (N = 239)		P*
	Median	Q₁-Q₃	Median	Q₁-Q₃	Median	Q₁-Q₃	Median	Q₁-Q₃	
Age (y)	58	50-64	51	45-59	52	45-61	62	57-66	
Years since diagnosis	ND	ND	44	39-56	26	19-34	10	4-17	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	
BMI†	26.7	6.6	26.6	4.4	27.1	5.2	28.1	5.4	
	N	%	N	%	N	%	N	%	
Sex: female	2503	53.3	27	34.2	130	64.0	152	63.6	
Allergic rhinitis	720	15.3	52	65.8	134	66.0	85	35.6	
Family history of asthma	985	21.0	34	43.0	95	46.8	104	43.5	
Smoking									
Never	2467	52.5	38	48.1	89	43.8	98	41.0	
Current	918	19.5	21	26.6	41	20.2	49	20.5	
Ex	1314	28.0	20	25.3	73	36.0	92	38.5	
Hypertension	1285	27.3	24	30.4	52	25.6	101	42.3	.12
Severe cardiovascular disease	327	7.0	6	7.6	11	5.4	30	12.6	.61
Coronary disease	163	3.5	1	1.3	1	0.5	15	6.3	.14
Heart failure	74	1.6	1	1.3	2	1.0	8	3.3	.55
Arrhythmia	359	7.6	8	10.1	18	8.9	38	15.9	.59
Stroke or TIA	135	2.9	4	5.1	9	4.4	14	5.9	.88
Diabetes	368	7.8	4	5.1	16	7.9	35	14.6	.26
Depression	447	9.5	9	11.4	37	18.2	42	17.6	.32
Anxiety or panic disorder	252	5.4	1	1.3	21	10.3	18	7.5	.10
GERD	323	6.9	12	15.2	30	14.8	44	18.4	.87
Chronic kidney failure	44	0.9	1	1.3	3	1.5	3	1.3	.89
Sleep apnea	227	4.8	5	6.3	18	8.9	26	10.9	.30
Osteoporosis	109	2.3	1	1.3	16	7.9	21	8.8	.34
Painful condition	405	8.6	7	8.9	32	15.8	51	21.3	.18
COPD	89	1.9	4	5.1	23	11.3	44	18.4	.06
Obesity†	930	20.2	18	23.4	46	22.9	73	31.1	.38
Nonrespiratory diseases ≥1†	2589	56.1	48	62.3	135	67.2	183	77.9	.28
Nonrespiratory diseases ≥2†	1327	28.8	24	31.2	84	41.8	130	55.3	.07
Nonrespiratory diseases ≥3†	653	14.2	13	16.9	39	19.4	88	37.4	**.01**

ND, Not defined; *Q₁-Q₃*, quartiles.
*Three diagnosis-age strata compared. Bolded text indicates statistical significance ($P < .017$).
†Missing= 85.

TABLE E2. Demographic characteristics, nonrespiratory diseases, and COPD, and statistical comparison between subjects with and without physician-diagnosed asthma

Variable	Without asthma (N = 7051)		Physician-diagnosed asthma (N = 879)		
	Median	**Q$_1$-Q$_3$**	**Median**	**Q$_1$-Q$_3$**	**P**
Age (y)	50	35-61	47	32-61	**.01**
Years since diagnosis	ND	ND	19	10-28	ND
Variable	**Mean**	**SD**	**Mean**	**SD**	
BMI*	26.0	6.4	26.7	5.3	**.001**
	N	**%**	**N**	**%**	
Sex: female	3855	54.7	498	56.7	.27
Allergic rhinitis	1275	18.1	508	57.8	**<.001**
Family history of asthma	1523	21.6	392	44.6	**<.001**
Smoking					**<.001**
Never	3838	54.4	409	46.5	
Current	1508	21.4	208	23.7	
Ex	1705	24.2	262	29.8	
Hypertension	1333	18.9	195	22.2	**.02**
Severe cardiovascular disease	344	4.9	50	5.7	.30
Coronary artery disease	165	2.3	18	2.0	.59
Arrhythmia	419	5.9	72	8.2	**.01**
Heart failure	87	1.2	13	1.5	.54
Stroke or TIA	140	2.0	27	3.1	**.03**
Diabetes	404	5.7	63	7.2	.09
Depression	733	10.4	133	15.1	**<.001**
Anxiety or panic disorder	427	6.1	81	9.2	**<.001**
GERD	399	5.7	103	11.7	**<.001**
Chronic kidney failure	51	0.7	7	0.8	.81
Sleep apnea	247	3.5	56	6.4	**<.001**
Osteoporosis	122	1.7	41	4.7	**<.001**
Painful condition	460	6.5	102	11.6	**<.001**
COPD	97	1.4	81	9.2	**<.001**
Obesity*	1152	16.6	302	23.2	**<.001**
No. of nonrespiratory diseases ≥1*	3260	47.0	508	58.7	**<.001**
No. of nonrespiratory diseases ≥2*	1558	22.5	288	33.3	**<.001**
No. of nonrespiratory diseases ≥3*	721	10.4	162	18.7	**<.001**

ND, Not defined; *Q$_1$-Q$_3$*, quartiles.
Bolded text indicates statistical significance (*P* < .05).
*Missing =126.

TABLE E3. Demographic characteristics, nonrespiratory diseases, and statistical comparison between subjects with and without physician-diagnosed asthma when subjects with COPD were excluded

Variable	Without asthma (N = 6954)		Physician-diagnosed asthma (N = 798)		
	Median	**Q₁-Q₃**	**Median**	**Q₁-Q₃**	**_P_**
Age (y)	49	35-61	45	32-60	**<.001**
Years since diagnosis	ND	ND	19	10-28	ND
Variable	**Mean**	**SD**	**Mean**	**SD**	
BMI*	26.0	6.4	26.6	5.2	**.001**
	N	**%**	**N**	**%**	
Sex: female	3808	54.8	459	57.5	.14
Allergic rhinitis	1248	17.9	466	58.4	**<.001**
Family history of asthma	1487	21.4	350	43.9	**<.001**
Smoking					**.003**
Never	3817	54.9	394	49.4	
Current	1469	21.1	171	21.4	
Ex	1668	24.0	233	29.2	
Hypertension	1295	18.6	163	20.4	.22
Severe cardiovascular disease	327	4.7	38	4.8	.94
Coronary artery disease	158	2.3	12	1.5	.16
Arrhythmia	80	1.2	58	7.3	.09
Heart failure	401	5.8	9	1.1	.96
Stroke or TIA	132	1.9	22	2.8	.10
Diabetes	389	5.6	48	6.0	.63
Depression	713	10.3	114	14.3	**<.001**
Anxiety or panic disorder	418	6.0	74	9.3	**<.001**
GERD	390	5.6	94	11.8	**<.001**
Chronic kidney failure	49	0.7	4	0.5	.51
Sleep apnea	233	3.4	47	5.9	**<.001**
Osteoporosis	113	1.6	34	4.3	**<.001**
Painful condition	440	6.3	82	10.3	**<.001**
Obesity*	1124	16.4	176	22.4	**<.001**
No. of nonrespiratory diseases ≥1*	3186	46.6	447	56.9	**<.001**
No. of nonrespiratory diseases ≥2*	1506	22.0	243	30.9	**<.001**
No. of nonrespiratory diseases ≥3*	691	10.1	133	16.9	**<.001**

_ND_, Not defined; _Q₁-Q₃_, quartiles.
Bolded text indicates statistical significance (_P_ < .05).
*Missing = 126.

TABLE E4. The risk of nonrespiratory diseases in subjects with early-, intermediate-, and late-diagnosed asthma vs subjects without asthma in univariate binary logistic regression analysis

Variable	Early-diagnosed asthma (0-11 y) OR (95 % CI)	*P*	Intermediate-diagnosed asthma (12-39 y) OR (95% CI)	*P*	Late-diagnosed asthma (40-69 y) OR (95% CI)	*P*
Hypertension	0.53 (0.36-0.80)	**.002**	0.83 (0.62-1.11)	.20	3.14 (2.41-4.09)	**<.001**
Severe cardiovascular disease	0.49 (0.22-1.11)	.087	0.62 (0.34-1.14)	.12	2.80 (1.88-4.17)	**<.001**
Arrhythmia	0.74 (0.40-1.37)	.34	0.99 (0.63-1.55)	.95	2.99 (2.09-4.29)	**<.001**
Stroke or TIA	0.82 (0.30-2.23)	.70	1.27 (0.64-2.52)	.49	3.07 (1.75-5.41)	**<.001**
Diabetes	0.41 (0.18-0.93)	**.034**	0.87 (0.54-1.41)	.58	2.82 (1.95-4.10)	**<.001**
Depression	1.16 (0.78-1.72)	.47	1.70 (1.27-2.27)	**<.001**	1.84 (1.31-2.59)	**<.001**
Anxiety or panic disorder	1.16 (0.70-1.91)	.57	2.12 (1.52-2.96)	**<.001**	1.26 (0.77-2.06)	.35
GERD	1.32 (0.81-2.16)	.27	1.92 (1.35-2.74)	**<.001**	3.76 (2.67-5.30)	**<.001**
Sleep apnea	0.81 (0.38-1.74)	.59	1.54 (0.96-2.49)	.076	3.36 (2.20-5.15)	**<.001**
Osteoporosis	0.23 (0.032-1.67)	.15	2.83 (1.69-4.76)	**<.001**	5.47 (3.38-8.86)	**<.001**
Painful condition	0.74 (0.41-1.33)	.31	1.60 (1.12-2.29)	**.010**	3.89 (2.81-5.37)	**<.001**
Obesity	1.07 (0.76-1.49)	.72	1.34 (1.03-1.75)	**.027**	2.26 (1.70-3.00)	**<.001**
COPD	2.42 (1.16-5.03)	**.018**	6.08 (3.94-9.40)	**<.001**	16.2 (11.0-23.7)	**<.001**
No. of nonrespiratory diseases ≥1	0.85 (0.65-1.10)	.21	1.47 (1.19-1.82)	**<.001**	3.97 (2.90-5.42)	**<.001**
No. of nonrespiratory diseases ≥2	0.71 (0.51-1.00)	**.050**	1.47 (1.16-1.86)	**.001**	4.27 (3.28-5.56)	**<.001**
No. of nonrespiratory diseases ≥3	0.70 (0.43-1.14)	.15	1.35 (0.98-1.84)	.063	5.16 (3.92-6.79)	**<.001**

Without asthma was coded as 0 and in each regression analysis, diagnosis-age stratum as 1. Bolded text indicates statistical significance (*P* < .05).

TABLE E5. The risk of nonrespiratory diseases in subjects with early-, intermediate-, and late-diagnosed asthma vs subjects without asthma in multivariable binary logistic regression analysis adjusted by age and sex, when subjects with COPD were excluded

Variable	Early-diagnosed asthma (0-11 y) OR (95% CI)	*P*	Intermediate-diagnosed asthma (12-39 y) OR (95% CI)	*P*	Late-diagnosed asthma (40-69 y) OR (95% CI)	*P*
Hypertension	1.55 (0.97-2.48)	.068	1.32 (0.94-1.86)	.11	1.46 (1.07-1.98)	**.017**
Severe cardiovascular disease	0.97 (0.39-2.46)	.95	1.20 (0.64-2.25)	.58	1.31 (0.80-2.15)	.29
Arrhythmia	1.25 (0.65-2.41)	.51	1.26 (0.77-2.07)	.36	1.82 (1.19-2.76)	**.005**
Stroke or TIA	1.61 (0.49-5.25)	.43	2.33 (1.15-4.71)	**.019**	1.61 (0.83-3.15)	.16
Diabetes	0.53 (0.19-1.45)	.22	1.10 (0.63-1.91)	.74	1.75 (1.14-2.68)	**.011**
Depression	1.04 (0.68-1.58)	.87	1.49 (1.09-2.04)	**.012**	2.00 (1.36-2.94)	**<.001**
Anxiety or panic disorder	1.12 (0.67-1.87)	.67	1.91 (1.34-2.71)	**<.001**	1.50 (0.85-2.54)	.17
GERD	1.88 (1.12-3.16)	**.016**	2.15 (1.47-3.14)	**<.001**	3.20 (2.21-4.63)	**<.001**
Sleep apnea	1.09 (0.47-2.53)	.84	2.47 (1.46-4.16)	**.001**	2.70 (1.64-4.46)	**<.001**
Osteoporosis	0.69 (0.09-5.01)	.71	3.44 (1.91-6.19)	**<.001**	3.00 (1.74-5.17)	**<.001**
Painful condition	1.23 (0.66-2.30)	.52	1.86 (1.26-2.75)	**.002**	2.27 (1.56-3.31)	**<.001**
Obesity	1.35 (0.95-1.94)	.10	1.55 (1.18-2.05)	**.002**	1.69 (1.23-2.33)	**.001**
No. of nonrespiratory diseases ≥1	1.46 (1.10-1.93)	**.008**	1.88 (1.49-2.38)	**<.001**	2.17 (1.54-3.05)	**<.001**
No. of nonrespiratory diseases ≥2	1.26 (0.87-1.82)	.23	1.90 (1.47-2.47)	**<.001**	2.47 (1.84-3.32)	**<.001**
No. of nonrespiratory diseases ≥3	1.28 (0.75-2.19)	.37	1.76 (1.23-2.50)	**.002**	3.17 (2.32-4.33)	**<.001**

Without asthma was coded as 0 and in each regression analysis, diagnosis-age stratum as 1. Bolded text indicates statistical significance (*P* < .05).