Original Article

Characterization of Asthma by Age of Onset: A Multi-Database Cohort Study

Esmé J. Baan, MD[a,*], Emmely W. de Roos, MD[b,c,*], Marjolein Engelkes, MD, PhD[a], Maria de Ridder, PhD[a], Lars Pedersen, PhD[d], Klara Berencsi, MD, PhD[d,e], Dani Prieto-Alhambra, MD, PhD[a,f,g], Francesco Lapi, PhD[h], Melissa K. Van Dyke, PhD[i], Peter Rijnbeek, PhD[a], Guy G. Brusselle, MD, PhD[b,c,j], and Katia M.C. Verhamme, MD, PhD[a,k] *Rotterdam, The Netherlands; Ghent, Belgium; Aarhus, Denmark; Oxford, United Kingdom; Barcelona, Spain; Florence, Italy; Collegeville, Pa*

What is already known? Differences in comorbidities by age of asthma onset have been reported, but most of these studies had modest sample sizes, were restricted to a single patient population, and did not differentiate between adult-onset asthma and late-onset asthma.

What does this study add? Patient characteristics and comorbidities vary by age of asthma onset. Furthermore, the age of onset and the level of asthma control are inversely related.

How will it affect current guidelines? Because age at asthma onset helps to phenotype asthma, the age of asthma onset should be considered when assessing asthma control and asthma management.

BACKGROUND: Asthma can occur at any age but the differences in patient characteristics between childhood-, adult-, and late-onset asthma are not well understood.
OBJECTIVE: To investigate differences in patients' characteristics by age at asthma onset.
METHODS: From 5 European electronic databases, we created a cohort encompassing adult patients with doctor-diagnosed asthma in 2008 to 2013. Patients were categorized based on their age at asthma onset: childhood-onset (age at onset < 18 y), adult-onset (age at onset 18−40 y), and late-onset asthma (age at onset ≥ 40 y). Comorbidities were assessed at study entry. For each characteristic and comorbidity, odds ratios and age- and sex-adjusted odds ratios (OR_{adj}) comparing asthma-onset categories were estimated per database and combined in a meta-analysis using a random effect model.
RESULTS: In total, 586,436 adult asthma patients were included, 81,691 had childhood-onset, 218,184 adult-onset, and 286,561 late-onset asthma. Overall, 7.3% had severe asthma.

[a]Department of Medical Informatics, Erasmus MC—University Medical Center Rotterdam, Rotterdam, The Netherlands
[b]Department of Epidemiology, Erasmus MC—University Medical Center Rotterdam, Rotterdam, The Netherlands
[c]Department of Respiratory Medicine, Ghent University Hospital, Ghent, Belgium
[d]Department of Clinical Epidemiology, Aarhus University Hospital, Aarhus, Denmark
[e]Musculoskeletal Pharmaco- and Device Epidemiology, Nuffield Department of Orthopaedics, Rheumatology, and Musculoskeletal Sciences (NDORMS), University of Oxford, Oxford, UK
[f]GREMPAL Research Group, Idiap Jordi Gol Primary Care Research Institute, CIBERFES ISCIII, Universitat Autonoma de Barcelona, Barcelona, Spain
[g]Centre for Statistics in Medicine, Nuffield Department of Orthopaedics, Rheumatology, and Musculoskeletal Sciences, University of Oxford, Oxford, UK
[h]Health Search, Italian College of General Practitioners and Primary Care, Florence, Italy
[i]Epidemiology, Value Evidence and Outcomes, Global R&D, GSK, Collegeville, Pennsylvania, USA
[j]Department of Respiratory Medicine, Erasmus MC—University Medical Center Rotterdam, Rotterdam, The Netherlands
[k]Department of Bioanalysis, Ghent University, Ghent, Belgium
* These authors contributed equally to the manuscript.

This project was supported by an unconditional research grant by GlaxoSmithKline (GSK) (PRJ2284).
Conflicts of interest: M. Engelkes reports grants from GSK during the conduct of the study. M. de Ridder reports grants from GSK during the conduct of the study. D. Prieto-Alhambra reports grants and other from AMGEN; grants, nonfinancial support, and other from UCB Biopharma; grants from Les Laboratoires Servier, outside the submitted work; and Janssen, on behalf of IMI-funded EHDEN and EMIF consortiums; and Synapse Management Partners have supported training programs organized by D. Prieto-Alhambra's department and open for external participants. F. Lapi reports grants from Chiesi, GSK, and Novartis during the conduct of the study. M. K. Van Dyke is a GSK employee and shareholder. P. Rijnbeek receives an unconditional grant from Janssen Research & Development and funding through the Innovative Medicines Initiative. G. G. Brusselle has received fees for advisory boards or lectures from AstraZeneca, Boehringer-Ingelheim, Chiesi, GlaxoSmithKline, Novartis, Sanofi, and Teva. K. M. C. Verhamme works for a research group that, in the past, received unconditional research grants from Yamanouchi, Pfizer/Boehringer Ingelheim, Novartis, Chiesi, Amgen, and UCB. The rest of the authors declare that they have no relevant conflicts of interest.
Received for publication June 27, 2021; revised March 14, 2022; accepted for publication March 15, 2022.
Available online April 8, 2022.
Corresponding author: Katia M. C. Verhamme, MD, PhD, Department of Medical Informatics—Erasmus MC, University Medical Center Rotterdam, P. O. Box 2040, Dr Molewaterplein 40, 3015, GD Rotterdam, The Netherlands. E-mail: k.verhamme@erasmusmc.nl.
2213-2198

https://doi.org/10.1016/j.jaip.2022.03.019

Abbreviations used
ACO- Asthma and chronic obstructive pulmonary disease overlap
ATC- Anatomical Chemical Classification
BMI- Body mass index
CPRD- Clinical Practice Research Datalink
DM- Diabetes mellitus
GERD- Gastroesophageal reflux disease
HSD- Health Search Database
ICS- Inhaled corticosteroids
IgE- Immunoglobulin E
IPCI- Integrated Primary Care Information Project
SIDIAP- Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària

Subjects with adult-onset compared with childhood-asthma had higher risks for overweight/obesity (OR_{adj} 1.4; 95% CI 1.1−1.8) and lower risks for atopic disorders (OR_{adj} 0.8; 95% CI 0.7−0.95). Patients with late-onset compared with adult-onset asthma had higher risks for nasal polyposis (OR_{adj} 1.8; 95% CI 1.2−2.6), overweight/obesity (OR_{adj} 1.3; 95% CI 1.2−1.4), gastroesophageal reflux disease (OR_{adj} 1.4; 95% CI 1.2−1.7), and diabetes (OR_{adj} 2.3; 95% CI 1.8−2.9). A significant association between late-onset asthma and uncontrolled asthma was observed (OR_{adj} 2.8; 95% CI 1.7−4.5). CONCLUSIONS: This international study demonstrates clear differences in comorbidities between childhood-, adult-, and late-onset asthma phenotypes in adults. Furthermore, patients with late-onset asthma had more frequent uncontrolled asthma. **(J Allergy Clin Immunol Pract 2022;10:1825-34)**

Key words: *Asthma; Age at onset; Adults; General population; Comorbidity; Epidemiology; Exacerbations*

INTRODUCTION

Asthma is an inflammatory chronic respiratory disease and affects approximately 5% of the adult population, with a lifetime risk of 34%.[1-3] Patients with asthma suffer from variable reversible airflow obstruction resulting in dyspnea, limitation of activity and/or productivity, and impaired quality of life.[4-6]

In the diagnosis and treatment of asthma, it is important to acknowledge its heterogeneous nature; asthma is regarded as an umbrella term for multiple phenotypes (ie, observable properties).[3,7,8] In current literature, the age of onset, namely the age of first manifestation of the disease, has been regarded as an important and clearly distinguishable marker for asthma phenotyping.[9-13] The definition of the age of asthma-onset categories varies between literature, but is usually viewed as childhood-onset or adult-onset (with various cutoff points such as 12, 16, or 18 y) and the more recently identified late-onset phenotype (from the age of 40 onward).[11] The clinical relevance of the age of onset is reflected in asthma prognosis (eg, lung function decline is steeper in persistent childhood onset asthma)[10] and differences in treatment response (eg, in a randomized controlled trial of reslizumab vs placebo, the reduction of asthma exacerbations in patients treated with reslizumab was higher in patients with late- vs early-onset asthma).[14]

Although other research groups already investigated differences in patient characteristics in relation to age at asthma onset, most of these studies had modest sample sizes, were restricted to a single patient population, and did not differentiate between adult-onset asthma and late-onset asthma. Few studies corrected for differences in age at time of observation.[11,12,15-17] This age adjustment is important when exploring the interaction between age at asthma onset and prevalence of comorbidities of interest. Insight into the relationship between asthma onset and comorbidities is needed because comorbidities can affect asthma control, the severity of asthma, the optimal choice of asthma treatment, and treatment response.[18]

We therefore investigated differences in patient characteristics in terms of demography and asthma-related comorbidities in 3 distinct asthma-onset categories—childhood-, adult-, and late-onset asthma—both in an overall adult asthma cohort and in a cohort of adult patients with severe asthma.

METHODS

Design and setting

For this observational study, we selected asthma cohorts from 5 different European databases: IPCI (Integrated Primary Care Information Project) from the Netherlands, HSD (Health Search Database) from Italy, CPRD (Clinical Practice Research Datalink) from the United Kingdom, SIDIAP (Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària) from Spain, and Aarhus (Aarhus University Prescription Database) from Denmark. Details on these databases have been described previously and are available in the Online Repository at www.jaci-inpractice.org.[19-24] These databases contain detailed information on patient characteristics, drug prescriptions or dispensing, diagnoses, comorbidities, and measurements (such as laboratory results) (Appendix E1; available in this article's Online Repository at www.jaci-inpractice.org). All participating databases comply with European Union guidelines on the use of medical data for research and are registered in the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) database.[25] The institutional review boards of the respective databases approved the study protocol prior to study initiation.

Study population

A cohort of patients with asthma was established in each database in the study period from January 1, 2008, to December 31, 2013. To enter the cohort, patients needed to be at least 18 years old, with a minimum of 1-year database history and at least 1 asthma-specific disease code in combination with prescriptions/dispensing of asthma drugs within 3 months before or after the entry of the asthma disease code (Tables E1 and E2; available in this article's Online Repository at www.jaci-inpractice.org).[26,27] Asthma drugs consisted of the following: inhaled corticosteroids (ICS), short-acting beta-2 agonists, long-acting beta-2 agonists, fixed combination of ICS + long-acting beta-2 agonists, leukotriene modifiers, short-acting muscarinic antagonists, fixed combination of short-acting beta-2 agonists + short-acting muscarinic antagonists, xanthines, systemic corticosteroids for the treatment of asthma, and anti−immunoglobulin E (IgE) treatment (omalizumab). Within the data sources, drugs are coded according to the Anatomical Chemical Classification (ATC) code of

the World Health Organization (WHO) and were extracted by an ATC-specific search on the drug exposure records.[28] Patients diagnosed with asthma and chronic obstructive pulmonary disease overlap (ACO) were excluded.[29]

Within the asthma cohort, a subcohort of patients with severe asthma was nested. According to international guidelines, severe asthma was defined as asthma requiring treatment with high-dose ICS plus a second asthma controller medication (and/or systemic corticosteroids).[30,31] To define high-dose ICS, we used cutoff values as suggested by Global Initiative for Asthma (GINA) guidelines.[31] Only those patients who used these drugs for a consecutive period of at least 120 days were included in the severe asthma subcohort. To account for time bias, the start date of severe asthma was set as day 120 of high-dose ICS use.

Onset of asthma

Based on the age of first asthma diagnosis as documented by the treating physician in the database, patients were classified as having either childhood-onset asthma, adult-onset asthma, or late-onset asthma. Childhood-onset asthma was defined as asthma diagnosis before the age of 18 years, adult-onset asthma as asthma diagnosis between 18 and 40 years, and late-onset asthma as asthma diagnosis from the age of 40 years onward.

Covariates

On the index date (first date of fulfilling all subcohort criteria), various characteristics and comorbidities in the patients' history were assessed: atopic disorder (allergic rhinitis, allergic conjunctivitis, atopic eczema/dermatitis) (Table E3; available in this article's Online Repository at www.jaci-inpractice.org),[32] chronic rhinosinusitis (Table E4; available in this article's Online Repository at www.jaci-inpractice.org), gastroesophageal reflux disease (GERD) (Table E5; available in this article's Online Repository at www.jaci-inpractice.org), nasal polyposis (Table E6; available in this article's Online Repository at www.jaci-inpractice.org), overweight/obesity (Table E7; available in this article's Online Repository at www.jaci-inpractice.org), diabetes mellitus (DM), smoking status, and history of asthma exacerbations (Table E2). Information on these comorbidities was extracted via an automated search on the presence of database-specific disease codes. A patient could have a history of more than 1 condition in the past—for instance, a patient could be labelled as having a history of allergic rhinitis as well as chronic rhinosinusitis. Overweight/obesity was based on either the presence of a disease code for overweight/obesity or body mass index (BMI) values greater than 25 (Table E8; available in this article's Online Repository at www.jaci-inpractice.org).

Uncontrolled asthma was defined as 2 or more severe asthma exacerbations (ie, need of a burst of systemic corticosteroids, emergency department visit, and/or hospitalization for asthma) in the year prior to the index date. Information on emergency room visits and/or hospitalization for asthma exacerbations was assessed based on the presence of disease codes or on information from referral and/or discharge letters (HSD, IPCI, and SIDIAP) for severe asthma exacerbations. If patients had less than 12 months prior to asthma diagnosis or the start of severe asthma, 1 exacerbation or more in the 6 months prior fulfilled the criterion. We also investigated age and sex as covariates.

Analysis

For each patient characteristic, the difference in prevalence between asthma-onset groups was tested, using binomial logistic regression models for dichotomous outcomes and multinomial logistic regression for the outcome smoking categories.

Because age is an important determinant of several characteristics to be analyzed, adjustment for age was performed. This was indeed needed because the age at study entry could be different from the age of asthma onset, because both incident and prevalent asthma patients were included. For instance, a patient with childhood-onset asthma would only enter the study from the age of 18 onward because our study population only considered adult patients.

In our dataset, when comparing the groups with childhood- and with late-onset asthma, there was only a small overlap of the distributions of age at index date. Therefore, the collinearity between age at index date and asthma-onset category was too strong to directly compare these 2 onset groups while also adjusting for age. Thus we opted for 2 separate comparisons: childhood-onset versus adult-onset asthma and adult-onset versus late-onset asthma.

In all analyses, each of the patient characteristics was used as the outcome and onset group (late-onset vs adult-onset asthma and adult-onset vs childhood-onset asthma) was the determinant. Models were adjusted for age and sex.

Estimated ORs from the 5 databases were meta-analyzed using a DerSimonian-Laird random-effects model.[33] Statistical analyses were conducted using R software, version 1.1.442, using the R metafor package for the meta-analyses.[34]

RESULTS

Cohort characteristics

In total, 586,436 asthma patients were included in the study: 81,691 (14%) of the subjects had childhood-onset asthma, 218,184 (37%) had adult-onset asthma, and 286,561 (49%) had late-onset asthma. The median age at study entry was higher in subjects with late-onset asthma (57−61 y depending on the database) than in patients with adult-onset asthma (28−45 y; $P < .0001$). Similarly, the median age at study entry was higher in adult-onset asthma than in childhood-onset asthma (median age 20−23 y; $P < .0001$) The proportion of females was highest in the late-onset asthmatics (61%−71%), lower in the adult-onset asthmatics (55%−60%), and lowest in the childhood-onset asthmatics (41%−48%) ($P < .001$) (Table I). Because the childhood-onset asthma subcohort in the SIDIAP database was very small (n = 623; 1% of the SIDIAP cohort), this SIDIAP childhood-onset subcohort was excluded from all analyses.

Severe asthma and uncontrolled asthma

In total, 42,611 patients (7.2%) with severe asthma were included (Table E9; available in this article's Online Repository at www.jaci-inpractice.org). The proportion of severe asthma was highest in the late-onset asthma subjects (10%; n = 28,309), lower in the adult-onset subjects (5%; n = 11,884), and lowest in the childhood-onset asthma subjects (3%; n = 2,418) (Figure 1A).

The percentage of uncontrolled asthma was 0.4% in childhood-onset asthma, 6% in adult-onset asthma, and 8% in late-onset asthma (Figure 1B). In patients with severe asthma, depending on the age of onset, the proportion of uncontrolled asthma was 4% to 7%.

Prevalence of comorbidities

The most common comorbidities were atopic disorder (31%) and overweight/obesity (50%). The prevalence of atopic disorder was highest in subjects with childhood-onset asthma (45%) and

TABLE I. Demographics, severe asthma, (un)controlled asthma, and comorbidities in asthma-onset groups

	Aarhus (Denmark) n = 14,041			CPRD (United Kingdom) n = 393,660			HSD (Italy) n = 37,003			IPCI (The Netherlands) n = 73,506			SIDIAP (Spain) n = 68,226		
Variables	**Childhood-onset**	**Adult-onset**	**Late-onset**	**Childhood-onset**	**Adult-onset**	**Late-onset**	**Childhood-onset**	**Adult-onset**	**Late-onset**	**Childhood-onset**	**Adult-onset**	**Late-onset**	**Childhood-onset**	**Adult-onset**	**Late-onset**
n (% of total cohort)	1,592 (11)	5,004 (36)	7,445 (53)	71,838 (18)	141,379 (36)	180,443 (46)	1,467 (4)	14,179 (38)	21,357 (58)	6,171 (8)	29,297 (40)	38,038 (52)	623 (1)	28,325 (42)	39,278 (58)
Age, median (minimum, maximum)	21 (18, 30)	35 (18, 52)	59 (40,102)	23 (18, 55)	36 (18, 63)	60 (40,109)	20 (18, 26)	33 (18, 48)	59 (40,107)	21 (18, 44)	34 (18, 58)	57 (40,105)	19 (18, 25)	31 (18, 46)	61 (40,104)
Females, %	45	59	61	44	59	62	41	54	64	48	60	62	47	55	71
Severe asthma, %	8.1	8.2	14.7	2.7	6.2	11.4	3.3	3.6	6.2	4.7	7.0	10.8	1.0	0.4	3.3
Controlled															
Yes, %	99.6	70.8	57.9	99.6	75.6	67.5	45.2	59.1	45.2	99.2	72.2	66.4	97.6	35.2	29.5
No, %	0.3	10.3	11.3	0.3	5.0	5.2	11.4	7.9	11.4	0.3	2.4	4.2	0.2	2.2	4.4
Undefined, %	0.1	18.9	30.9	0.1	19.4	27.3	43.4	33.0	43.4	0.5	25.4	29.4	2.2	62.6	66.1
Atopic disorder, %	20.3	22.2	9.2	20.3	39.5	28.7	12.9	21.5	12.9	42.9	36.3	24.7	19.9	21.7	13.9
Chronic sinusitis, %	0.1	0.2	0.4	0.1	8.0	11.2	1.8	1.5	1.8	2.1	2.7	3.4	0.0	0.5	0.7
Diabetes, %	0.5	1.9	6.0	0.5	1.9	9.5	9.9	0.9	9.9	0.5	1.7	11.7	0.2	0.7	11.9
GERD, %	0.6	2.2	5.1	0.6	6.4	13.2	14.3	7.5	14.3	1.9	4.0	9.1	0.2	0.9	2.8
Nasal polyposis, %	0.3	1.0	2.1	0.3	1.7	4.6	1.3	0.8	1.3	0.2	0.3	0.6	0.3	0.8	1.8
Obesity, %	2.2	9.3	10.5	2.2	54.7	72.2	24.3	15.0	24.3	9.6	17.2	36.1	17.8	31.4	64.3
Smoking															
Current, %	0.0	0.8	1.0	0.0	27.5	14.8	12.9	16.5	12.9	11.2	16.8	13.9	21.8	27.1	13.2
Never, %	0.0	1.0	2.4	0.0	45.4	42.4	34.7	25.1	34.7	20.5	24.0	33.1	35.8	33.5	56.1
Past, %	0.0	0.3	1.7	0.0	26.5	42.5	12.6	4.4	12.6	3.5	9.1	17.7	1.9	8.5	12.3
Unknown, %	100.0	98.0	95.0	100.0	0.7	0.2	39.7	54.0	39.7	64.9	50.2	35.3	40.4	30.9	18.4

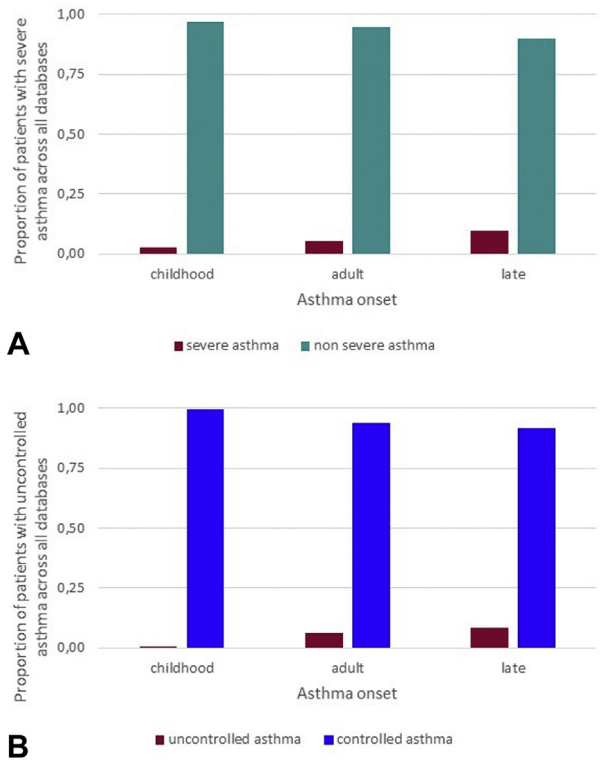

FIGURE 1. (**A**) Percentage of severe asthma across all databases by age of onset. (**B**) Level of control across all databases by age of onset in patients with ≥ 1 year of asthma history (uncontrolled asthma: ≥2 severe asthma exacerbations [ie, systemic corticosteroid course, emergency department visit, and/or hospitalization for asthma] in the year prior to the index date).

decreased to 35% in adult-onset and 25% in late-onset asthma, whereas the prevalence of overweight/obesity increased from childhood-onset asthma (30%) toward adult-onset asthma (43%) and late-onset asthma (61%). Chronic rhinosinusitis, DM, GERD, and nasal polyposis were less common with prevalence ranging between 2% and 8% (Figure 2).

Database-specific proportions of severe and uncontrolled asthma and comorbidities are described in Table I.

Comparison of asthma-onset groups

Comparing childhood-onset asthma and adult-onset asthma. Subjects with adult-onset asthma had significantly more uncontrolled asthma than subjects with childhood-onset asthma (meta-analysis results: OR 15.8 [95% CI 9.5−26.3]; OR_{adj} 43.1 [95% CI 20.6−89.8]). Adult-onset asthmatics had significantly less frequent atopic disorders (OR_{adj} 0.8 [95% CI 0.7−0.9]). Patients with adult-onset asthma also had more frequent nasal polyposis, DM, GERD, and overweight/obesity; however, upon age and sex adjustment, the only comorbidity that remained significantly different was overweight/obesity (OR_{adj} 1.4 [95% CI 1.1−1.8]). In both the crude and the adjusted analyses, adult-onset asthmatics were significantly more often current smokers (OR_{adj} 1.5 [95% CI 1.2−1.9]) or past smokers (OR_{adj} 1.7 [95% CI 1.3−2.2]) than childhood-onset asthmatics (Table II, Figure 3, and Figure E1; available in this article's Online Repository at www.jaci-inpractice.org).

Comparing childhood-onset asthma and adult-onset asthma in the subcohort with severe asthma. In patients with severe asthma, those with adult-onset asthma had significantly more uncontrolled asthma than childhood-onset asthma (OR 2.1 [95% CI 1.2−3.5]; OR_{adj} 3.2 [95% CI 1.8−5.8]). Severe asthma patients with adult-onset asthma also had significantly more frequent nasal polyposis, DM, GERD, and overweight/obesity than severe asthmatics with childhood-onset asthma. However, after adjustment, only overweight/obesity occurred significantly more often in adult-onset asthma (Table E10 and Figure E2; available in this article's Online Repository at www.jaci-inpractice.org).

Comparing adult-onset asthma and late-onset asthma. When adjusting for age and sex, subjects with late-onset asthma had significantly more uncontrolled asthma than those with adult-onset asthma (OR_{adj} 2.8 [95% CI 1.7−4.5]). Subjects with late-onset asthma had less frequent atopic disorders and were more likely to have chronic rhinosinusitis, although these differences did not remain significant after adjustment for age and sex. Compared with adult-onset asthma patients, late-onset asthmatics were significantly more likely to have nasal polyposis, DM, and GERD, and they were more often obese and past smokers. (Table II, Figure 3, and Figure E3; available in this article's Online Repository at www.jaci-inpractice.org)

Comparing adult-onset asthma and late-onset asthma within severe asthma. In subjects with severe asthma, again the odds of having atopic disorders were lower in those with late-onset asthma than in those with adult-onset asthma, and the odds of nasal polyposis, overweight/obesity, DM, and GERD were higher for late-onset asthma. The associations remained similar after adjustment for age and sex, except that the odds of having atopic disorders in late-onset asthmatics was less strong, resulting in OR_{adj} of 0.8 (95% CI 0.6−0.9) and also the association with GERD could no longer be observed (Table E10 and Figure E1).

DISCUSSION

In this large international cohort study encompassing more than 580,000 asthma patients from 5 European countries, several key findings have direct implications for clinical practice. First, patient characteristics and comorbidities in subjects with asthma vary significantly by age of asthma onset. Indeed, in adults with late-onset asthma, nasal polyposis, overweight/obesity, GERD, and DM were more frequent than in adults with an earlier asthma onset, even when corrected for age. Second, we confirm a distinct sex pattern according to age at onset of asthma, with a male predominance in patients with childhood-onset asthma and a female predominance in patients with adult-onset asthma and especially in those with late-onset asthma. Third, not only comorbidity and sex but also asthma control varied considerably by age of asthma onset, because lack of asthma control (defined by the occurrence of 2 or more exacerbations in the previous year) was significantly more frequent in patients with late-onset asthma and adult-onset asthma than in subjects with childhood-onset asthma. Lastly, severe asthma (defined by the use of high-dose ICS in combination with use of a second controller) was most prevalent in patients with late-onset asthma.

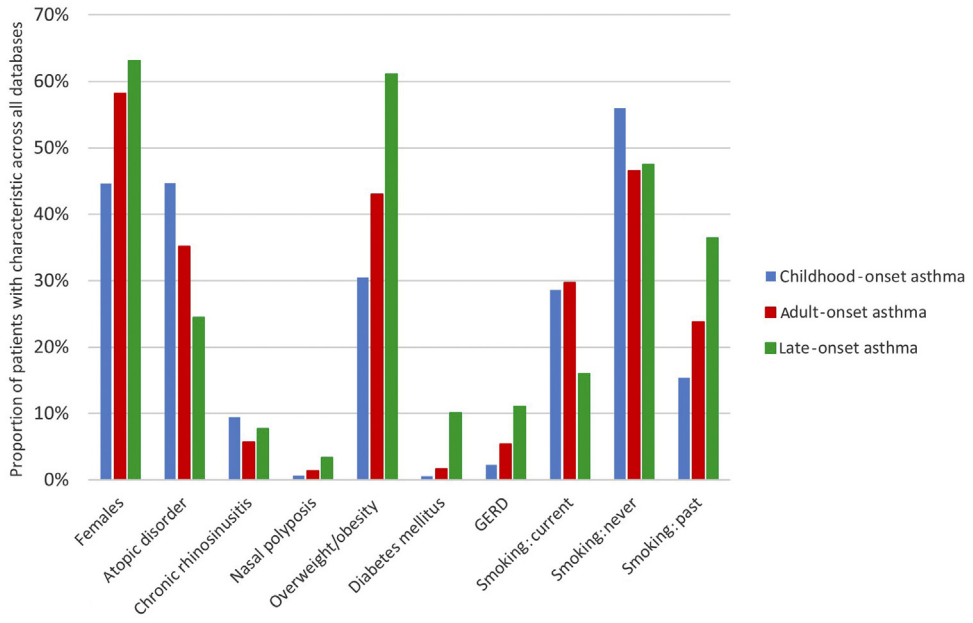

FIGURE 2. Prevalence of patient characteristics across all databases by age of onset. GERD, Gastroesophageal reflux disease.

TABLE II. OR of having various characteristics, meta-analysis result of crude and adjusted models

	Adult- vs childhood-onset							
	Crude model				Adjusted model*			
Variables	OR	95%	CI	*P* value	OR	95%	CI	*P* value
Uncontrolled asthma	15.80	9.48	26.31	<.0001	**43.05**	**20.64**	**89.81**	**<.0001**
Atopic disorder	0.82	0.74	0.91	.0001	**0.81**	**0.69**	**0.95**	**.0084**
Chronic rhinosinusitis	1.08	0.68	1.74	.7347	**0.56**	**0.33**	**0.95**	**.0299**
Nasal polyposis	2.41	2.15	2.70	<.0001	1.04	0.79	1.37	.7863
Overweight/obesity	2.37	1.96	2.86	<.0001	**1.38**	**1.08**	**1.76**	**.0090**
Diabetes mellitus	3.32	3.01	3.66	<.0001	0.90	0.80	1.02	.0944
GERD	2.73	2.24	3.33	<.0001	1.30	0.97	1.74	.0771
Smoking: current	1.45	1.15	1.82	.0016	**1.51**	**1.21**	**1.89**	**.0003**
Smoking: past	2.54	1.84	3.49	<.0001	**1.73**	**1.34**	**2.23**	**<.0001**
	Late- vs adult-onset							
	Crude model				Adjusted model*			
	OR	95%	CI	*P* value	OR	95%	CI	*P* value
Uncontrolled asthma	1.68	1.24	2.27	.0007	**2.77**	**1.69**	**4.53**	**.0001**
Atopic disorder	0.53	0.49	0.59	<.0001	0.92	0.72	1.17	.4832
Chronic rhinosinusitis	1.37	1.22	1.53	<.0001	1.13	0.87	1.47	.3486
Nasal polyposis	2.13	1.72	2.64	<.0001	**1.76**	**1.19**	**2.61**	**.0047**
Overweight/obesity	2.17	1.62	2.91	<.0001	**1.29**	**1.20**	**1.38**	**<.0001**
Diabetes mellitus	7.84	4.98	12.36	<.0001	**2.28**	**1.82**	**2.87**	**<.0001**
GERD	2.34	2.14	2.57	<.0001	**1.42**	**1.20**	**1.69**	**.0001**
Smoking: current	0.49	0.36	0.67	<.0001	**1.51**	**1.16**	**1.97**	**.0024**
Smoking: past	1.55	1.13	2.11	.0061	**1.59**	**1.12**	**2.26**	**.0094**

Bold indicates statistical significance.
*Adjusted model includes adjustment for age and sex.

Studying age-specific asthma phenotypes is important because differences in the prevalence of asthma has been related to age-associated hormonal changes, especially in women.[9,16,35] Indeed, boys more often have asthma than girls and, after puberty, these incidences reverse.[36] We observed that this female predominance was even stronger in late-onset asthma, which of course, cannot be attributed to puberty. Data on differences in asthma incidence during menopause are conflicting because a

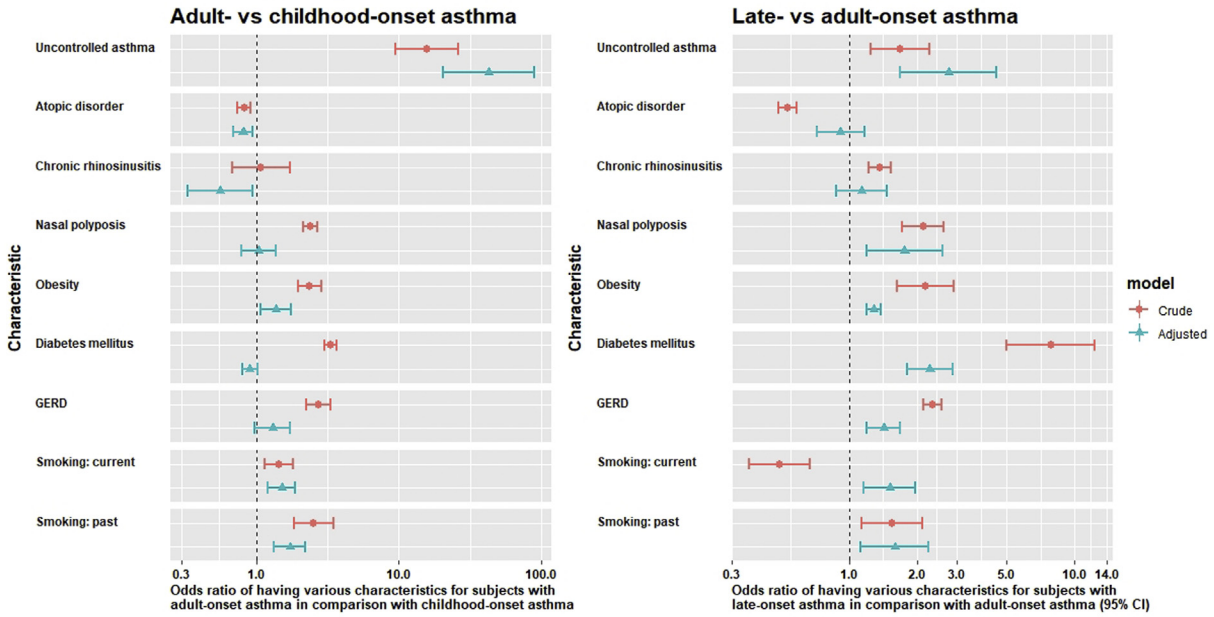

FIGURE 3. Odds ratio of having various characteristics, meta-analysis result. Adjusted for age and sex. GERD, gastroesophageal reflux disease. Uncontrolled asthma is defined as ≥ 2 severe asthma exacerbations (ie, systemic corticosteroid course, emergency department visit, or hospitalization for asthma) in the one year prior to index date

decrease in asthma prevalence after menopause has been reported in The Nurses' Health Study,[37] whereas in the French E3N cohort, an increased asthma risk was demonstrated after surgical menopause.[38] Recently, the group of Shah et al[39] performed a cohort study of more than 300,000 women, with a follow-up time of up to 17 years, using data from the Optimum Patient Care Research Database (OPCRD); they reported that use of hormone replacement therapy reduced the risk of late-onset asthma in menopausal women with more than 15%. This risk decreased by dose and duration of use. In the accompanying editorial, the mechanisms behind this association were further elaborated, including a possible role for endogenous and exogenous reproductive hormones in the sex-specific asthma expression across the lifespan.[40] Nwaru et al,[41] using a subcohort of the study by Shah et al,[39] further investigated the role of hormone replacement therapy in women with asthma and observed that past use (but not current use) was associated with an increased risk of severe asthma exacerbations. The role of sex hormones in the pathogenesis of asthma is thus complex and requires further research. We are not the first indicating that the prevalence of atopic disorders decreases with increasing age of asthma onset. Indeed, Pakkasela et al[42] recently reported that the nonallergic component (absence of allergic rhinitis) became much more dominant from the age of 40 years. Similarly Agondi et al[43] reported as well that atopy was inversely correlated with age of asthma onset. Whereas the prevalence of atopic disorders decreased, the prevalence of overweight/obesity, GERD, and DM were more frequent in late-onset asthma than in an earlier asthma onset, even when corrected for age. Similar results were recently reported from the Tasmanian Longitudinal Health Study in which individuals with asthma 7 to 53 years old were invited in the last follow-up (at age of 53 years) and were questioned whether they had ever been diagnosed with specific comorbidities of interest.[44] The late-onset asthma trajectory was predominantly associated with multiple disorders including diabetes, GERD, and obesity.[44]

In subjects with late-onset asthma, 8% suffered frequent exacerbations. This confirms recent findings reporting that this late-onset asthma potentially poses a higher risk for asthma exacerbations and hospitalizations than childhood-onset asthma.[36,45,46] Exacerbations are detrimental for lung function and quality of life, and acute treatment consists of oral corticosteroid courses that cause multiple side effects. Prevention of exacerbations is therefore key in asthma management, and the high percentages of frequent exacerbators in late-onset asthma subjects as reported in this manuscript and others underline the importance of targeting this specific population.[31]

In severe asthma cohorts, asthma and nasal pathologies are strongly associated, that is, rhinosinusitis is associated with the onset of asthma in adults.[47] Although the underlying mechanism has yet to be further elucidated, our findings further strengthen these associations between nasal polyposis and late-onset asthma on a population level. Similar to our data, Staniorski et al[48] showed increased prevalence of nasal polyposis in those with adult- or late-onset asthma than in childhood-onset asthmatics.[48] Lastly, in line with previous findings in smaller studies, our data show that, with increasing age of asthma onset, the prevalence of allergic conditions decreases.[49,50]

As for all observational studies, our study has strengths and limitations. A major strength is the fact that we included a large number of patients from 5 different European databases that collect detailed information on important covariates such as lifestyle factors, drug exposure, and underlying comorbidities. In addition, our results represent real-life data, hence increasing the external validity of the findings. Our report is unique in the sense that 3 groups are studied, whereas previous studies only

compared 2 age-at-onset groups, had a smaller sample size, and did not adjust for age.[11,12,15-17]

In our study, it is statistically correct to compare the groups, because the age distribution of the childhood-onset group in our dataset has enough overlap in age with the adult-onset group. This makes it possible to adjust for age between the childhood-onset and the adult-onset group and similarly for comparison between the adult-onset and the late-onset group. We believe that age adjustment comparison between these groups, albeit in a 2-step approach, is a very relevant addition to the current literature.

This study also has limitations. First, misclassification of the age of asthma onset, especially in subjects with childhood asthma, is possible if patients do not recall the correct age of asthma onset or in case general practice software systems do not allow entering of historical dates. This concern was also raised in the review article by Dharmage et al[51] stating that, for adults, prospectively collected data on childhood asthma status will minimize the risk of recall bias; otherwise retrospective recall typically misclassifies relapsed childhood asthma as late-onset asthma and will preferentially favor those who have more severe childhood disease. This potential misclassification might explain why less than 14% of the adult asthmatics have a record of an asthma diagnosis before the age of 18 years. Based on literature, we would assume that the proportion of patients with childhood-onset asthma would be larger. In a recent review article by Trivedi and Denton[52] on the differences in asthma in children versus adults, approximately half of middle-aged patients with asthma had childhood-onset rather than adult-onset asthma; however, this proportion decreased in older study populations. The proportion of childhood asthma as reported in the cross-sectional study by To et al,[53] who investigated differences in clinical characteristics among patients with adult-onset, childhood-persistent, or childhood-relapsing asthma was 28%. Although this proportion of childhood-onset asthma was higher than the proportion we reported, it is lower than the 50% reported by Trivedi and Denton,[52] but the median age of the population by To et al[53] ranged between 42 and 62 years, again highlighting the effect of age at study entry.

Further, comorbidities were assessed through an automatic search on disease codes, which might give rise to misclassification. For example, owing to the granularity of disease coding, we were not always able to distinguish chronic rhinosinusitis from allergic rhinitis. However, it is unlikely that this misclassification would differentiate between the onset groups. Also, we probably underestimated the prevalence of atopy because information on IgE levels and results of allergy skin prick tests was not available on all patients. Ideally, the diagnosis of atopy would be confirmed by allergen-specific IgE levels and/or allergy skin prick tests, but this information was not available in all patients within the different databases; moreover, if available, this information was often only available as free text and not as coded data. As a proxy for atopy, we searched for disease codes related to atopic eczema/dermatitis and allergic rhinitis/conjunctivitis and labeled this as atopic disorders similar to what other research groups have done.[32,54]

This study was investigated in a group of patients with asthma only in which patients with ACO were excluded. This was a well-considered choice in view of potential misclassification between asthma and chronic obstructive pulmonary disease, which is presumably higher in older patients (and thus those patients with late-onset asthma).

Lastly, in the cross-sectional design of the current study, we could not infer direction of the effects, that is, overweight/obesity can be both a risk factor for asthma development as well as an asthma-associated comorbidity.[47,55] This, however, does not mitigate the relevance of associations between age at onset of asthma and comorbidities we report because awareness is relevant on both the policy-making and the patient care levels.

There is not a strict definition of age cutoffs to define childhood-onset, adult-onset, and late-onset asthma. Indeed, age cutoffs for early- onset asthma vary between 10 and 21 years of age and for late-onset mostly between 40 and 45 years, with some reports using 65 years,[11,15-17] which makes comparison with other studies challenging. We opted for 18 years to discern childhood-onset asthma from adult-onset asthma, and we applied the commonly used age of 40 as the second cutoff to discriminate adult-onset asthma from late-onset asthma. Further research is needed to explore different age cutoffs and ideally come to a unanimous definition. This should be combined with research into the biological explanations behind the reported age differences.

Our results have clinical implications because, from our data, asthma can be described in many phenotypes of which age of asthma onset might be an important one with regard to underlying comorbidity, asthma control, and asthma severity that might be due to treatment response.[56] Especially the increasing proportion of frequent exacerbators with increasing age of onset must be an incentive to strive for optimal asthma control in these patients.

Because we conducted a cross-sectional analysis, we cannot conclude whether asthma (exacerbations) could be prevented by targeting comorbidities such as nasal polyposis, GERD, and DM. However, it would be very relevant to investigate the possible synergistic treatment effect of 1 comorbid condition on asthma control and *vice versa*. In general, smoking and weight management (through physical activity, exercise, and healthy diet) can be regarded as modifiable targets not only for the prevention of asthma in adulthood but also for many other noncommunicable chronic diseases. Overall, our findings of common comorbidities in subjects with asthma call for management of these conditions, not only to reduce directly their burden of disease but also to, we hope, improve asthma control.

In conclusion, this international multi-database cohort study demonstrates consistent differences in asthma-related comorbidities, asthma control (ie, exacerbation rates), and severity of asthma between childhood-onset, adult-onset, and late-onset phenotypes of adult asthmatics. Further research on the pathophysiological basis of these differences might give better insights into the clinical utility of these phenotypes toward personalized asthma management.

REFERENCES

1. The Global Asthma Report 2014—Global Burden of Disease due to Asthma. The Global Asthma Report 2014. Auckland, New Zealand: Global Asthma Network; 2014.
2. To T, Wang C, Guan J, McLimont S, Gershon AS. What is the lifetime risk of physician-diagnosed asthma in Ontario, Canada? Am J Respir Crit Care Med 2010;181:337-43.
3. Wenzel SE. Asthma phenotypes: the evolution from clinical to molecular approaches. Nature Med 2012;18:716.
4. Besen E, Pranksy G. Assessing the relationship between chronic health conditions and productivity loss trajectories. J Occup Environ Med 2014;56:1249-57.

5. Papi A, Brightling C, Pedersen SE, Reddel HK. Asthma. Lancet 2018;391:783-800.
6. Vermeulen F, Garcia G, Ninane V, Laveneziana P. Activity limitation and exertional dyspnea in adult asthmatic patients: what do we know? Respir Med 2016;117:122-30.
7. Haldar P, Pavord ID, Shaw DE, Berry MA, Thomas M, Brightling CE, et al. Cluster analysis and clinical asthma phenotypes. Am J Respir Crit Care Med 2008;178:218-24.
8. Ilmarinen P, Tuomisto LE, Niemela O, Tommola M, Haanpaa J, Kankaanranta H. Cluster analysis on longitudinal data of patients with adult-onset asthma. J Allergy Clin Immunol Pract 2017;5:967-978.e3.
9. Khusial RJ, Sont JK, Loijmans RJB, Snoeck-Stroband JB, Assendelft PJJ, Schermer TRJ, et al. Longitudinal outcomes of different asthma phenotypes in primary care, an observational study. NPJ Prim Care Respir Med 2017;27:55.
10. Tan DJ, Walters EH, Perret JL, Burgess JA, Johns DP, Lowe AJ, et al. Clinical and functional differences between early-onset and late-onset adult asthma: a population-based Tasmanian Longitudinal Health Study. Thorax 2016;71:981-7.
11. Tan DJ, Walters EH, Perret JL, Lodge CJ, Lowe AJ, Matheson MC, et al. Age-of-asthma onset as a determinant of different asthma phenotypes in adults: a systematic review and meta-analysis of the literature. Expert Rev Respir Med 2015;9:109-23.
12. Baptist AP, Ross JA, Clark NM. Older adults with asthma: does age of asthma onset make a difference? J Asthma 2013;50:836-41.
13. Miranda C, Busacker A, Balzar S, Trudeau J, Wenzel SE. Distinguishing severe asthma phenotypes: role of age at onset and eosinophilic inflammation. J Allergy Clin Immunol 2004;113:101-8.
14. Brusselle G, Germinaro M, Weiss S, Zangrilli J. Reslizumab in patients with inadequately controlled late-onset asthma and elevated blood eosinophils. Pulm Pharmacol Ther 2017;43:39-45.
15. Hekking PP, Loza MJ, Pavlidis S, de Meulder B, Lefaudeux D, Baribaud F, et al. Pathway discovery using transcriptomic profiles in adult-onset severe asthma. J Allergy Clin Immunol 2018;141:1280-90.
16. Sood A, Qualls C, Schuyler M, Arynchyn A, Alvarado JH, Smith LJ, et al. Adult-onset asthma becomes the dominant phenotype among women by age 40 years. the longitudinal CARDIA study. Ann Am Thorac Soc 2013;10:188-97.
17. Lange P, Colak Y, Ingebrigtsen TS, Vestbo J, Marott JL. Long-term prognosis of asthma, chronic obstructive pulmonary disease, and asthma-chronic obstructive pulmonary disease overlap in the Copenhagen City Heart study: a prospective population-based analysis. Lancet Respir Med 2016;4:454-62.
18. Yawn BP, Han MK. Practical considerations for the diagnosis and management of asthma in older adults. Mayo Clin Proc 2017;92:1697-705.
19. Cazzola M, Puxeddu E, Bettoncelli G, Novelli L, Segreti A, Cricelli C, et al. The prevalence of asthma and COPD in Italy: a practice-based study. Respir Med 2011;105:386-91.
20. Cricelli C, Mazzaglia G, Samani F, Marchi M, Sabatini A, Nardi R, et al. Prevalence estimates for chronic diseases in Italy: exploring the differences between self-report and primary care databases. J Public Health Med 2003;25:254-7.
21. Ehrenstein V, Antonsen S, Pedersen L. Existing data sources for clinical epidemiology: Aarhus University Prescription Database. Clin Epidemiol 2010;2:273-9.
22. Gulliford MC, van Staa T, Dregan A, McDermott L, McCann G, Ashworth M, et al. Electronic Health Records for Intervention Research: a cluster randomized trial to reduce antibiotic prescribing in primary care (eCRT Study). Ann Fam Med 2014;12:344-51.
23. Vlug AE, van der Lei J, Mosseveld BM, van Wijk MA, van der Linden PD, Sturkenboom MC, et al. Postmarketing surveillance based on electronic patient records: the IPCI project. Methods Inf Med 1999;38:339-44.
24. Sorensen HT, Larsen BO. A population-based Danish data resource with possible high validity in pharmacoepidemiological research. J Med Syst 1994;18:33-8.
25. Kurz X, Perez-Gutthann S, ENCePP Steering Group. Strengthening standards, transparency, and collaboration to support medicine evaluation: ten years of the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP). Pharmacoepidemiol Drug Saf 2018;27:245-52.
26. Kerkhof M, Tran TN, Soriano JB, Golam S, Gibson D, Hillyer EV, et al. Healthcare resource use and costs of severe, uncontrolled eosinophilic asthma in the UK general population. Thorax 2018;73:116-24.
27. Nissen F, Morales DR, Mullerova H, Smeeth L, Douglas IJ, Quint JK. Validation of asthma recording in the Clinical Practice Research Datalink (CPRD). BMJ Open 2017;7:e017474.
28. Hollingworth S, Kairuz T. Measuring medicine use: applying ATC/DDD methodology to real-world data. Pharmacy (Basel) 2021;9:60.
29. van den Berge M, Aalbers R. The asthma-COPD overlap syndrome: how is it defined and what are its clinical implications? J Asthma Allergy 2016;9:27-35.
30. Chung KF, Wenzel SE, Brozek JL, Bush A, Castro M, Sterk PJ, et al. International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma. Eur Respir J 2014;43:343-73.
31. Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention. GINA. Accessed April 26, 2022. https://ginasthma.org/gina-reports/gina-2020-full-report_-final-_wms/
32. Pols DHJ, Bohnen AM, Nielen MMJ, Korevaar JC, Bindels PJE. Risks for comorbidity in children with atopic disorders: an observational study in Dutch general practices. BMJ Open 2017;7:e018091.
33. DerSimonian R, Laird N. Meta-analysis in clinical trials revisited. Contemp Clin Trials 2015;45:139-45.
34. Viechtbauer W. Conducting meta-analyses in R with the metafor package. J Statistic Softw 2010;36:1-48.
35. Melgert BN, Ray A, Hylkema MN, Timens W, Postma DS. Are there reasons why adult asthma is more common in females? Curr Allergy Asthma Rep 2007;7:143-50.
36. Vink NM, Postma DS, Schouten JP, Rosmalen JG, Boezen HM. Gender differences in asthma development and remission during transition through puberty: the TRacking Adolescents' Individual Lives Survey (TRAILS) study. J Allergy Clin Immunol 2010;126. 498-504.e1-6.
37. Troisi RJ, Speizer FE, Willett WC, Trichopoulos D, Rosner B. Menopause, postmenopausal estrogen preparations, and the risk of adult-onset asthma. A prospective cohort study. Am J Respir Crit Care Med 1995;152:1183-8.
38. Matulonga-Diakiese B, Courbon D, Fournier A, Sanchez M, Bedard A, Mesrine S, et al. Risk of asthma onset after natural and surgical menopause: results from the French E3N cohort. Maturitas 2018;118:44-50.
39. Shah SA, Tibble H, Pillinger R, McLean S, Ryan D, Critchley H, et al. Hormone replacement therapy and asthma onset in menopausal women: national cohort study. J Allergy Clin Immunol 2021;147:1662-70.
40. Wright RJ. Hormones and women's respiratory health across the lifespan: windows of opportunity for advancing research. J Allergy Clin Immunol 2021;147:1643-5.
41. Nwaru BI, Shah SA, Tibble H, Pillinger R, McLean S, Ryan D, et al. hormone replacement therapy and risk of severe asthma exacerbation in perimenopausal and postmenopausal women: 17-year national cohort study. J Allergy Clin Immunol Pract 2021;9:2751-27560.e1.
42. Pakkasela J, Ilmarinen P, Honkamaki J, Tuomisto LE, Andersen H, Piirila P, et al. Age-specific incidence of allergic and non-allergic asthma. BMC Pulm Med 2020;20:9.
43. Agondi RC, Andrade MC, Takejima P, Aun MV, Kalil J, Giavina-Bianchi P. Atopy is associated with age at asthma onset in elderly patients? J Allergy Clin Immunol Pract 2018;6:865-71.
44. Bui DS, Lodge CJ, Perret JL, Lowe A, Hamilton GS, Thompson B, et al. Trajectories of asthma and allergies from 7 years to 53 years and associations with lung function and extrapulmonary comorbidity profiles: a prospective cohort study. Lancet Respir Med 2021;9:387-96.
45. Bloom CI, Nissen F, Douglas IJ, Smeeth L, Cullinan P, Quint JK. Exacerbation risk and characterisation of the UK's asthma population from infants to old age. Thorax 2018;73:313-20.
46. Mirabelli MC, Beavers SF, Chatterjee AB, Moorman JE. Age at asthma onset and subsequent asthma outcomes among adults with active asthma. Respir Med 2013;107:1829-36.
47. Kankaanranta H, Kauppi P, Tuomisto LE, Ilmarinen P. Emerging comorbidities in adult asthma: risks, clinical associations, and mechanisms. Mediators Inflamm 2016;2016:3690628.
48. Staniorski JC, Price CPE, Weibman AR, Welch KC, Conley DB, Shintani-Smith S, et al. Asthma onset pattern and patient outcomes in a chronic rhinosinusitis population. Int Forum Allergy Rhinol 2018;8:495-503.
49. Chaudhuri R, McSharry C, Heaney LG, Niven R, Brightling CE, Menzies-Gow AN, et al. Effects of older age and age of asthma onset on clinical and inflammatory variables in severe refractory asthma. Respir Med 2016;118:46-52.
50. Herscher ML, Wisnivesky JP, Busse PJ, Hanania NA, Sheng T, Wolf MS, et al. Characteristics and outcomes of older adults with long-standing versus late-onset asthma. J Asthma 2017;54:223-9.

51. Dharmage SC, Perret JL, Custovic A. Epidemiology of asthma in children and adults. Front Pediatr 2019;7:246.
52. Trivedi M, Denton E. Asthma in children and adults—what are the differences and what can they tell us about asthma? Front Pediatr 2019;7:256.
53. To M, Tsuzuki R, Katsube O, Yamawaki S, Soeda S, Kono Y, et al. Persistent asthma from childhood to adulthood presents a distinct phenotype of adult asthma. J Allergy Clin Immunol Pract 2020;8. 1921-7.e2.
54. Pols DH, Wartna JB, Moed H, van Alphen EI, Bohnen AM, Bindels PJ. Atopic dermatitis, asthma and allergic rhinitis in general practice and the open population: a systematic review. Scand J Prim Health Care 2016;34:143-50.
55. Holguin F. Obesity as a risk factor for increased asthma severity and allergic inflammation; cause or effect? Clin Exp Allergy 2012;42:612-3.
56. Kaplan A, Szefler SJ, Halpin DMG. Impact of comorbid conditions on asthmatic adults and children. NPJ Prim Care Respir Med 2020;30:36.

ONLINE REPOSITORY APPENDIX E1

Description of Databases

The Integrated Primary Care Information (IPCI) database is a Dutch database containing the complete medical record of more than 2.5 million patients provided by more than 640 general practitioners (GPs; 374 practices) geographically spread over the Netherlands.[E1] The demographics of patients included in IPCI are representative of the Dutch population. In the Netherlands, all citizens are registered with a GP practice that acts as a gatekeeper in a 2-way exchange of information with secondary care. The medical records can, therefore, be assumed to contain all relevant medical information including medical findings and diagnosis from secondary care. The International Classification of Primary Care (ICPC) is the coding system but diagnoses and complaints can also be entered as free text. Prescription data contain information on product name, quantity prescribed, dosage regimens, strength, indication, and Anatomical Chemical Classification (ATC) codes.

The Health Search Database (HSD) is a longitudinal observational database that is representative of the Italian general population. The HSD contains data from computer-based patient records from a selected group of GPs (covering a total of 1.5 million patients) located throughout Italy. The database includes information on age, gender, patient, and GP identification, which is linked to prescription information, clinical events and diagnoses, and date of death. All diagnoses are coded according to the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM). Drug names are coded according to the ATC classification.[E2,E3] Comparing the regional distribution of the population HSD with the resident population in Italy as of January 1, 2017, surveyed by ISTAT (Italian National Institute of Statistics), a substantial overlap emerges between the 2 populations. The distribution by gender and age group of the HSD population results are superimposable on the general population estimated by ISTAT (https://report.healthsearch.it/Report_XII.pdf).

Clinical Practice Research Datalink (CPRD) is a large validated computerized database of anonymized longitudinal medical records for primary care. The CPRD operates a general practice opt-in and patient opt-out system. The GP practices choose to contribute deidentified patient data to CPRD for all patients, with the exception of those who have opted-out from the sharing of their patient record with CPRD. The CPRD collects deidentified patient data from a network of primary care practices (PCPs) across the United Kingdom. Primary care data are linked to a range of other health-related data to provide a longitudinal, representative U.K. population health dataset. The data encompass 50 million patients, including 16 million currently registered patients. The database contains the entire anonymized electronic medical record of each patient, including medical codes associated with consultations and referrals; details of all medications prescribed; lifestyle factors, and laboratory tests.[E4] Information on hospitalization is collected through linkage Hospital Episode Statistics (HES) and information on mortality is retrieved through linkage with the Office of National Statistics Mortality data.

The Aarhus University Prescription Database comprises clinical and prescription data from the Central Denmark Region and the North Denmark Region. This population covers a total of 1.2 million inhabitants and is representative of the population of Denmark.[E5] Data are available on demographics, lifestyle factors, dispensing data, hospitalizations, and procedures. Dispensing data comprise the filled prescriptions for all ambulatory patients and contain information on the name of the drug, ATC code, package identifier (strength and route of administration), and date of refill. These data are linked to the national registry of patients that comprises information on admissions to Danish somatic hospitals, emergency rooms and outpatient clinics, diagnosis codes and procedures.

The primary care structure in Catalonia comprises 358 primary care practices (PCPs) composed of health professionals and support staff who are responsible for the health care of the population in their assigned geographic area. The Catalan Institute of Health manages 274 PCPs (76.5%); the remaining centers are managed by other health care entities. Each PCP has at least 3 (and an average of 12) basic care units, defined as 1 GP and 1 nurse providing care for an assigned set of patients. The SIDIAP Database comprises the electronic medical records of a representative sample of patients attended by GPs in Catalonia (North-East Spain), covering a population of more than 5.1 million patients (about 80% of the total of 7.5 million population of Catalonia) from 274 PCPs. The SIDIAP data comprise the clinical and referral events (coded by ICD-10), demography information, prescription and dispensing, specialist referrals, lifestyle factors, laboratory test results, and hospital admissions and their major outcomes.[E6] The SIDIAP covers more than 80% of the Catalan residents and, therefore, is unsurprisingly representative of the source population. This has been shown in many instances.[E6-E9]

Description of Terms and Database Codes (ICD/READ/ICPC)

Asthma. Concepts of disease have been mapped through the Unified Medical Language System (UMLS) for asthma (Table E1).

Asthma exacerbation

Definition of severe asthma exacerbation. Asthma exacerbation was defined as the use of acute systemic corticosteroids, emergency department visit, or hospitalization for reasons of asthma exacerbation. To identify patients with a severe asthma exacerbation defined as emergency department visit or hospitalization for reasons of asthma, an automated search was done on codes specific for severe asthma exacerbation. In addition, the medical file was searched for asthma-specific disease codes (thus, not only asthma exacerbation codes) in combination with codes for hospitalization. Hospitalization was retrieved either via linkage with hospital admission/discharge database (Aarhus, CPRD [→ HES]), combination of disease codes with information from hospital referral (HSD, SIDIAP and IPCI) and discharge letters (SIDIAP and IPCI), or combination of disease codes with source codes (hospital discharge letters) (CPRD → for those patients where we did not have HES).

Disease codes also did fit the criteria of asthma exacerbation (Table E2)

Atopic disorders. Atopic disorder is defined as any of the following: atopic dermatitis/eczema or allergic rhinitis.

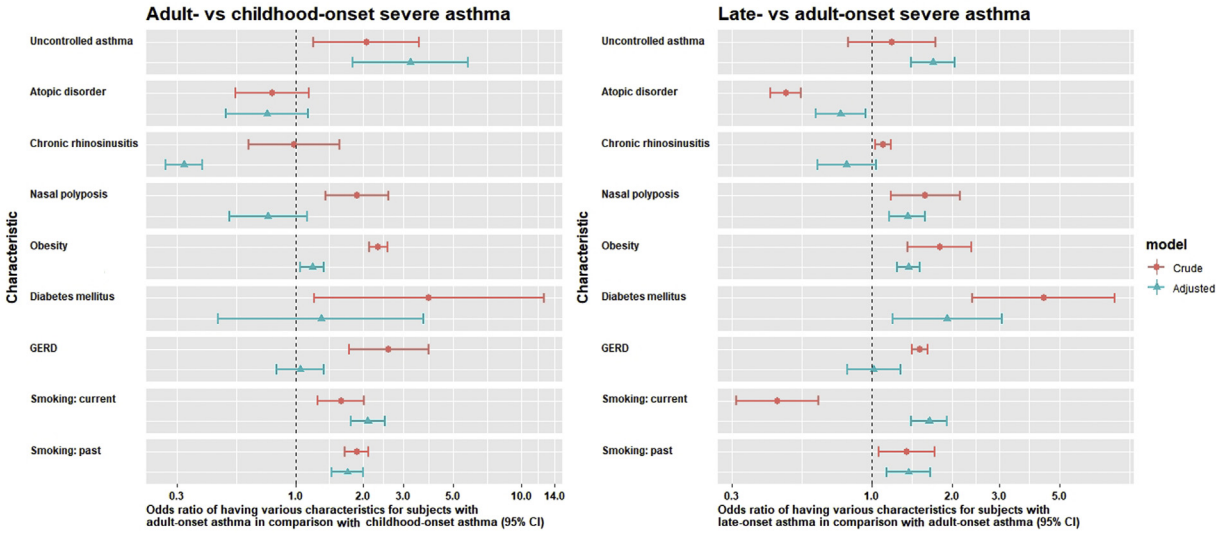

FIGURE E1. OR of having various characteristics in the cohort of patients with severe asthma, The adjusted OR of the meta-analysis is provided. This adjusted OR means that the result was adjusted for age and sex. Uncontrolled asthma is defined as $\geq$ 2 severe asthma exacerbations (ie, systemic corticosteroid course, emergency department visit, or hospitalization for asthma) in the year prior to the index date.

Concepts of disease have been mapped through the UMLS for atopy (Table E3).

Chronic rhinosinusitis. Concepts of disease have been mapped through the UMLS for chronic rhinosinusitis (Table E4).

Gastroesophageal reflux disease. Concepts of disease have been mapped through the UMLS for gastroesophageal disease (GERD) (Table E5).

Nasal polyposis. Concepts of disease have been mapped through the UMLS for nasal polyps (Table E6).

Overweight and obesity. Concepts of disease have been mapped through the UMLS for obesity (Table E7).

In addition, body mass index (BMI) was retrieved from the measurement table in all databases.

Cutoff BMI values for obesity or overweight are shown in Table E8.

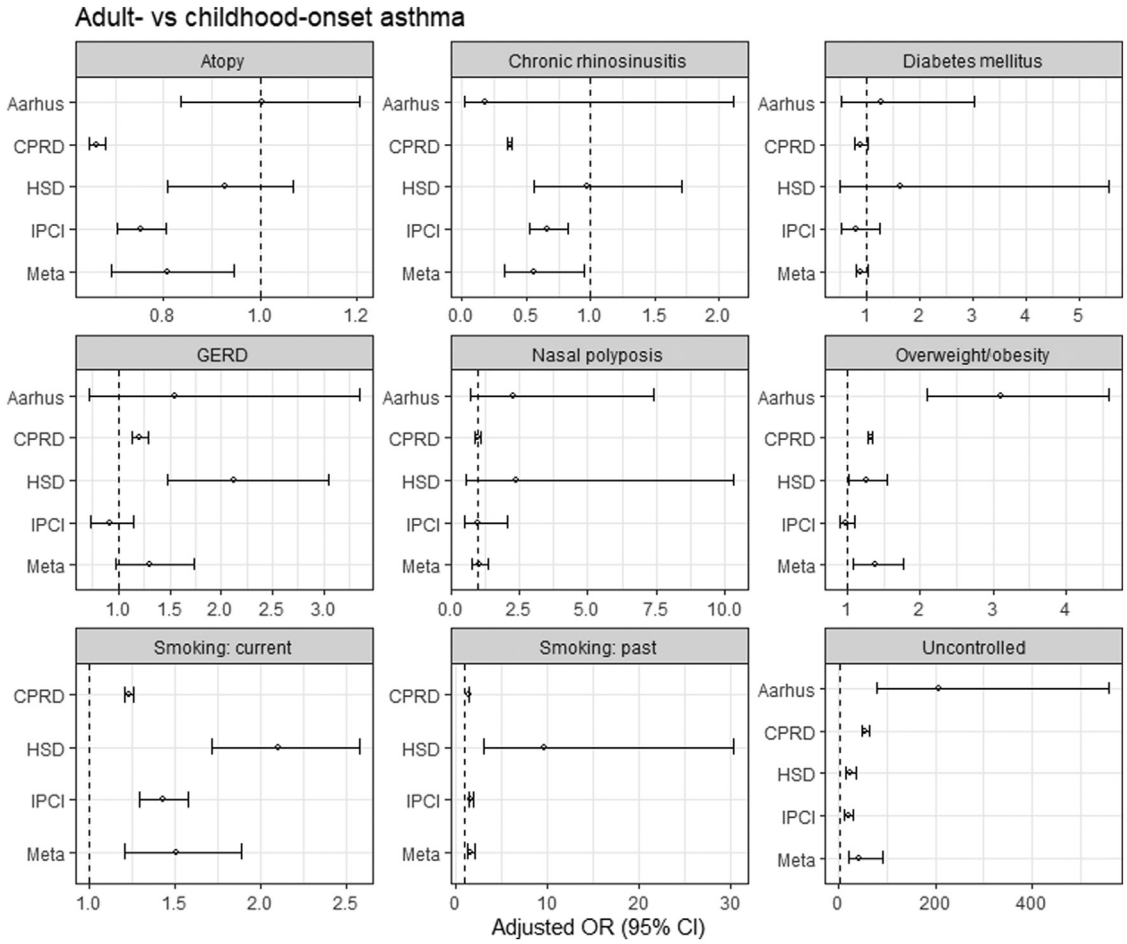

FIGURE E2. OR of having various characteristics for adult- vs childhood-onset asthma. Adjusted ORs are provided by database as well as the meta-analysis (Meta) results. This adjusted OR means that there was adjustment for age and sex. Uncontrolled asthma is defined as $\geq$ 2 severe asthma exacerbations (ie, systemic corticosteroid course, emergency department visit or hospitalization for asthma) in the year prior to the index date.

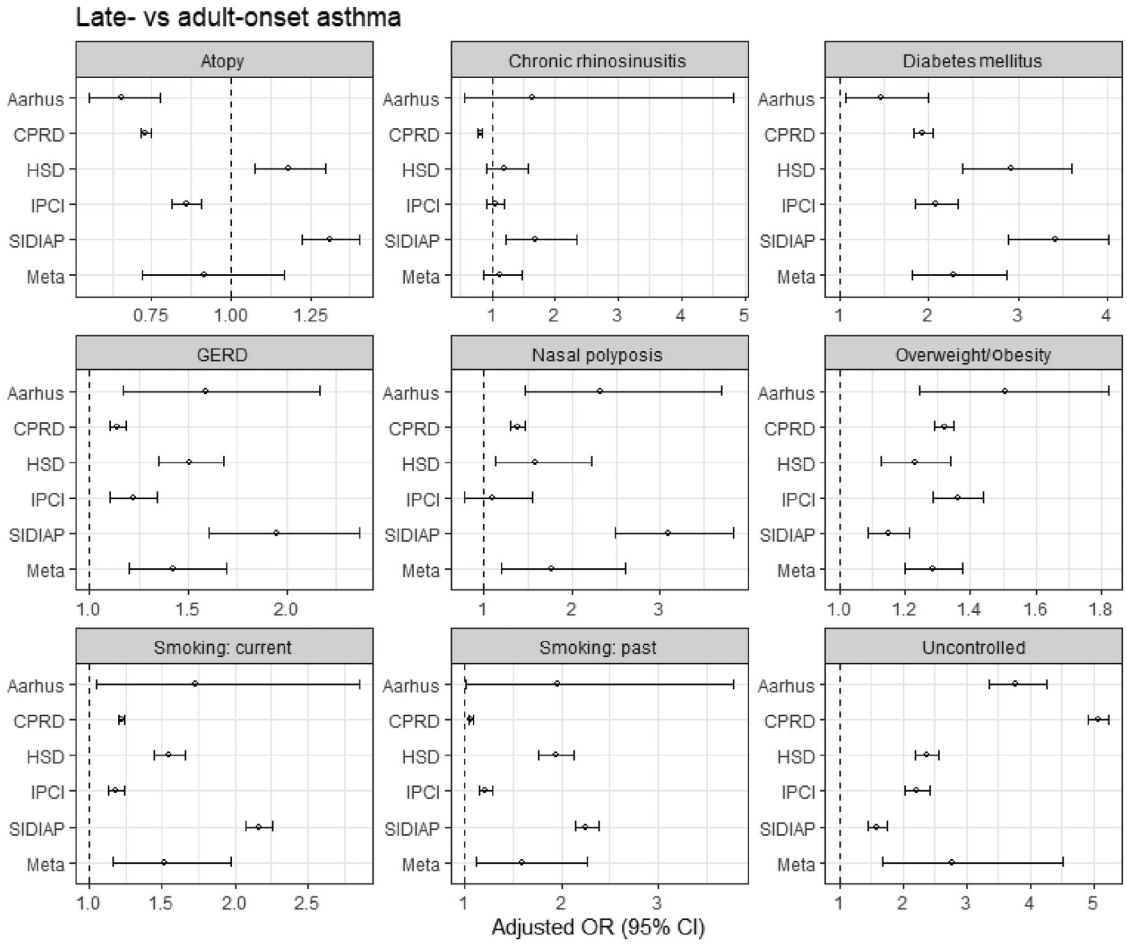

FIGURE E3. OR of having various characteristics for late- vs adult-onset asthma. Adjusted ORs are provided by database as well as the meta-analysis (Meta) results. This adjusted OR means that there was adjustment for age and sex. Uncontrolled asthma is defined as $\geq$ 2 severe asthma exacerbations (ie, systemic corticosteroid course, emergency department visit or hospitalization for asthma) in the year prior to the index date.

TABLE E1. Asthma disease codes

Terms	ICD-10	ICD-9-CM	Read Codes	ICPC
Asthma	J45*	493*	H33*	R96
Asthma confirmed			1O2.00	
Extrinsic asthma with asthma attack			663d.00	
			663m.00	
Asthma severity			663V*	
Number of asthma exacerbations in past year			663y.00	
Emergency admission. asthma			8H2P.00	
Status asthmaticus	J46			
Induced asthma			173A.00	
Asthma trigger			173c.00	
			173d.00	
			178*.00	
Asthma accident and emergency attendance since last visit			663m.00	
Emergency asthma admission since last appointment			663d.00	
Asthma and exercise			663e.00	
			663e000	
			663e100	
			663f.00	
			663w.00	
			663x.00	
Asthma currently dormant			663h.00	
Asthma currently active			663j.00	
Asthma treatment compliance satisfactory			663n.00	
Asthma treatment compliance unsatisfactory			663p.00	
Asthma disturbing sleep			663N.00	
Asthma causing night waking			663N000	
Asthma disturbs sleep weekly			663N100	
Asthma disturbs sleep frequently			663O.00	
Asthma not disturbing sleep			663O000	
Asthma never disturbs sleep			66YP.00	
Asthma night-time symptoms			66Yq.00	
Asthma causes night-time symptoms			66Yr.00	
Asthma causes symptoms most nights			66Ys.00	
Asthma never causes night symptoms				
Asthma limits activities			663P*	
Asthma daytime symptoms			663q.00	
Asthma not limiting activities			663Q.00	
Asthma causes night symptoms 1 to 2 times per mo			663r.00	
Asthma never causes daytime				
symptoms			663s.00	
Asthma causes daytime symptoms 1 to 2 times per mo			663t.00	
Asthma causes daytime symptoms 1 to 2 times per wk			663u.00	
Asthma causes daytime symptoms			663v.00	
Asthma prophylactic medication used			663W.00	
Asthma medication review			8B3j.00	
Absent from work or school owing to asthma			66YC.00	
Number days absent from school owing to asthma in past 6 mo			66Yu.00	
Health education—asthma			679J.00*	
Asthma control			8793.00	
			8794.00	
			8795.00	
			8796.00	
			8797.00	
			8798.00	
Asthma quality indicators			9hA*.00	

*All codes falling under this category.

TABLE E2. Asthma exacerbation disease codes

Terms	ICD-10	ICD-9-CM	Read Codes	ICPC
Emergency admission: asthma			8H2P.00	
Status asthmaticus	J46	493.01	H33z000	
	J45.22	493.11		
	J45.32	493.21		
	J45.42	493.91		
	J45.52			
	J45.902			
Severe asthma attack			H33z011	
Asthma accident and emergency attendance since last visit			663m.00	
Emergency asthma admission since last appointment			663d.00	

TABLE E3. Disease codes for atopy

Terms	ICD-10	ICD-9-CM	Read Codes	ICPC
Atopic dermatitis/ eczema	L20*	691*	M111.00	S87
			M112.00	
			M113.00	
			M114.00	
			M11z.00	
Allergic rhinitis	J30* (excluding J30.0)	477*	H17*	R97
			H120.11	
Asthma with allergic rhinitis (nasal congestion)	J45.909			
Other allergic rhinitis			Hyu2100	
			Hyu2000	
Allergic eczema			M114.00	

*All codes falling under this category.

TABLE E4. Disease codes for chronic rhinosinusitis

Terms	ICD-10	ICD-9-CM	Read Codes	ICPC
Chronic rhinitis			H120*	
Chronic allergic sinusitis			H13.11	R75.02
Allergic sinusitis			H17.00	
Other chronic sinusitis			Hyu2200	
Chronic sinusitis, unspecified	J32.9	473.9		
Chronic sinusitis			H13*	
Allergic rhinosinusitis			H17.12	

*All codes falling under this category.

TABLE E5. Disease codes for GERD

Terms	ICD-10	ICD-9-CM	Read Codes	ICPC
Gastroesophageal reflux disease (GERD)	K21*	530.81		
Reflux esophagitis			J101100	
Acid reflux			J101111	
Gastroesophageal reflux with esophagitis	K21.0	530.81	J101112	
Gastroesophageal reflux without esophagitis	K21.9	530.81	J101112	
Esophageal reflux with esophagitis		530.11	J101113	D84.03
Esophageal reflux without (mention) of esophagitis			J10y400	D84.02
Esophageal reflux	K21.9		J10y411	
Gastroesophageal reflux	K21.9		J10y412	
Acid reflux	K21.9	530.81	J10y413	
Peptic esophagitis			J101114	
Regurgitant esophagitis			J101115	
Gastric reflux			1957.00	

*All codes falling under this category.

TABLE E6. Disease codes for nasal polyps

Terms	ICD-10	ICD-9-CM	Read Codes	ICPC
Nasal polyps	J33*	471*	H11*	R99.02
Nasal polyp present			2D33.00	
Nasal polypectomy			7406000	
			7402900	
			7402911	
			7406700	
			7416F00	

*All codes falling under this category.

TABLE E7. Disease codes for overweight/obesity

Terms	ICD-10	ICD-9-CM	Read Codes	ICPC
Overweight/obesity BMI > 30	E66*	278.0*	C38*	T83
Adipositas				T82
BMI > 40.0–44.9	Z68.4*	278.01	22K7.00	
BMI 45.0–49.9	Z68.42			
BMI > 30		V85.3*	22K5.00	
BMI 85th < 95th percentile	Z68.53	V85.53		
BMI ≥ 95th percentile	Z68.54	V85.54		
Other obesity			Cyu7*	

*All codes falling under this category.

TABLE E8. Cutoff BMI values for obesity or overweight

Variable	Adults (>19)
Obese	BMI $\geq$ 30
Overweight	BMI between 25 and 29.9

TABLE E9. Demographics of asthma-onset groups—severe asthma cohort

Variable	Database	Childhood-onset asthma n = 2,418	Adult-onset asthma n = 11,884	Late-onset asthma n = 28,309
Aarhus	n (% of onset group)	129 (8.1)	409 (8.2)	1,095 (14.7)
	Age (y), median (range)	21 (18−30)	40 (19−52)	61 (40−95)
	Females, %	40	67	62
CPRD	n (% of onset group)	1,947 (2.7)	8,781 (6.2)	20,486 (11.4)
	Age (y), median (range)	24 (18−55)	40 (18−64)	65 (40−101)
	Females, %	50	62	64
HSD	n (% of onset group)	49 (3.3)	515 (3.6)	1,331 (6.2)
	Ag (y), median (range)	22 (18−27)	36 (20−51)	63 (40−102)
	Females, %	45	50	63
IPCI	n (% of onset group)	289 (4.7)	2,060 (7.0)	4,097 (10.8)
	Age (y), median (range)	21 (18−45)	37 (19−57)	58 (40−97)
	Females, %	53	61	64
SIDIAP	n (% of onset group)	4 (0.6)	119 (0.4)	1,300 (3.3)
	Age (y), median (range)	22 (19−24)	37 (20−45)	71 (40−97)
	Females, %	50	56	71

TABLE E10. Odds ratio of having various characteristics, meta-analysis result adjusted for age and sex (severe asthma)

	Adult- vs childhood-onset (severe asthma)							
	Crude model				Adjusted model			
Variable	OR	95%	CI	P value	OR	95%	CI	*P* value
Uncontrolled asthma	2.06	1.20	3.53	.0085	3.24	1.80	5.82	.0001
Atopic disorder	0.79	0.54	1.15	.2138	0.75	0.49	1.14	.1730
Chronic rhinosinusitis	0.99	0.62	1.57	.9644	0.32	0.27	0.39	<.0001
Nasal polyposis	1.87	1.35	2.57	.0001	0.76	0.51	1.12	.1653
Overweight/obesity	2.33	2.12	2.56	<00001	1.19	1.05	1.34	.0051
Diabetes mellitus	3.90	1.21	12.57	.0229	1.30	0.46	3.69	.6254
GERD	2.59	1.73	3.87	<.0001	1.05	0.83	1.34	.6809
Smoking: current	1.59	1.26	2.01	.0001	2.09	1.76	2.49	<.0001
Smoking: past	1.87	1.65	2.11	<.0001	1.70	1.45	1.99	<.0001
	Late- vs adult-onset (severe asthma)							
	Crude model				Adjusted model			
	OR	95%	CI	*P* value	OR	95%	CI	*P* value
Uncontrolled asthma*	1.19	0.81	1.73	.3696	1.69	1.40	2.05	<.0001
Atopic disorder	0.48	0.42	0.55	<.0001	0.77	0.62	0.95	.0154
Chronic rhinosinusitis	1.10	1.03	1.18	.0060	0.81	0.63	1.04	.0923
Nasal polyposis	1.59	1.18	2.14	.0026	1.36	1.17	1.58	.0001
Overweight/obesity	1.79	1.36	2.35	<.0001	1.37	1.25	1.51	<.0001
Diabetes mellitus	4.37	2.37	8.05	<.0001	1.91	1.20	3.05	.0066
GERD	1.51	1.41	1.61	<.0001	1.02	0.81	1.28	.8825
Smoking: current	0.44	0.31	0.63	<.0001	1.63	1.40	1.91	<.0001
Smoking: past	1.35	1.06	1.72	.0154	1.37	1.13	1.66	.0011

*Uncontrolled asthma is defined as $\geq$ 2 severe asthma exacerbations (ie, systemic corticosteroid course, emergency department visit, or hospitalization for asthma) in the year prior to the index date.

REFERENCES

E1. Vlug AE, van der Lei J, Mosseveld BM, van Wijk MA, van der Linden PD, Sturkenboom MC, et al. Postmarketing surveillance based on electronic patient records: the IPCI project. Methods Inf Med 1999;38:339-44.

E2. Cazzola M, Puxeddu E, Bettoncelli G, Novelli L, Segreti A, Cricelli C, et al. The prevalence of asthma and COPD in Italy: a practice-based study. Respir Med 2011;105:386-91.

E3. Cricelli C, Mazzaglia G, Samani F, Marchi M, Sabatini A, Nardi R, et al. Prevalence estimates for chronic diseases in Italy: exploring the differences between self-report and primary care databases. J Public Health Med 2003;25:254-7.

E4. Gulliford MC, van Staa T, Dregan A, McDermott L, McCann G, Ashworth M, et al. Electronic health records for intervention research: a cluster randomized trial to reduce antibiotic prescribing in primary care (eCRT Study). Ann Fam Med 2014;12:344-51.

E5. Ehrenstein V, Antonsen S, Pedersen L. Existing data sources for clinical epidemiology: Aarhus University Prescription Database. Clin Epidemiol 2010;2:273-9.

E6. García-Gil MDM, Hermosilla E, Prieto-Alhambra D, Fina F, Rosell M, Ramos R, et al. Construction and validation of a scoring system for the selection of high-quality data in a Spanish population primary care database (SIDIAP). Inform Prim Care 2011;19:135-45.

E7. Violan C, Foguet-Boreu Q, Hermosilla-Perez E, Valderas JM, Bolibar B, Fabregas-Escurriola M, et al. Comparison of the information provided by electronic health records data and a population health survey to estimate prevalence of selected health conditions and multimorbidity. BMC Public Health 2013;13:251.

E8. Ramos R, Ballo E, Marrugat J, Elosua R, Sala J, Grau M, et al. Validity for use in research on vascular diseases of the SIDIAP (Information System for the Development of Research in Primary Care): the EMMA study. Rev Esp Cardiol (Engl Ed) 2012;65:29-37.

E9. Bolíbar B, Fina Avilés F, Morros R, García-Gil MDM, Hermosilla E, Ramos R, et al. SIDIAP database: electronic clinical records in primary care as a source of information for epidemiologic research [in Spanish]. Med Clin (Barc) 2012;138:617-21.