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Long-term prognosis of new adult-onset asthma in obese patients

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Obese patients with new adult-onset asthma often remain obese in the long-term and have more exacerbations and respiratory-related hospital admissions during follow-up. High priority should be given to weight loss during treatment to prevent this outcome. https://bit.ly/2G5HtRZ

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ABSTRACT

Background: Obesity has been associated with poor outcomes of asthma in cross-sectional studies, but long-term effect of obesity on asthma remains unknown.

Aims: To study the effects of obesity, found at the time of diagnosis of adult-onset asthma, on 12-year prognosis by focusing on oral corticosteroid (OCS) use and respiratory-related hospital admissions.

Methods: Patients diagnosed with adult-onset asthma (n=203) were divided into three categories based on diagnostic body mass index (BMI) (<25 kg·m^{-2}, 25–29.9 kg·m^{-2}, ⩾30 kg·m^{-2}) and followed for 12 years as part of the Seinäjoki Adult Asthma Study. Self-reported and dispensed OCS were assessed for the 12-year period. Data on hospital admissions were analysed based on medical records.

Results: 12 years after diagnosis, 86% of the patients who were obese (BMI ⩾30 kg·m^{-2}) at diagnosis remained obese. During the follow-up, no difference was found in weight gain between the BMI categories. During the 12-year follow-up, patients obese at diagnosis reported more frequent use of OCS courses (46.9% *versus* 23.1%, p=0.028), were dispensed OCS more often (81.6% *versus* 56.9%, p=0.014) and at higher doses (median 1350 (interquartile range 280–3180) mg *versus* 600 (0–1650) mg prednisolone, p=0.010) compared to normal-weight patients. Furthermore, patients who were obese had more often one or more respiratory-related hospitalisations compared to normal-weight patients (38.8% *versus* 16.9%, p=0.033). In multivariate logistic regression analyses, obesity predicted OCS use and hospital admissions.

Conclusions: In adult-onset asthma, patients obese at diagnosis mostly remained obese at long-term and had more exacerbations and respiratory-related hospital admissions compared to normal-weight patients during 12-year follow-up. Weight loss should be a priority in their treatment to prevent this outcome.

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This study is registered at www.ClinicalTrials.gov with identifier number NCT02733016. All data generated or analysed during this study are included in this published article (and its supplementary files). According to ethical permission and patient data-protection laws of Finland, single patient data cannot be made available.

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Introduction

Obesity has been suggested as a risk factor for adult-onset asthma [1–3]. It has been proposed to associate with poor outcomes of asthma, such as poor disease control, increased use of oral steroids, urgent visits to healthcare and lower lung function, but the results are not consistent [4–7]. In addition, adverse effects of obesity on asthma are supported by the existence of an obesity-related phenotype, identified by many cluster analyses [8–10]. This phenotype is characterised by frequent symptoms and exacerbations, use of high-dose inhaled corticosteroids (ICS), but normal eosinophil count [3, 8–10].

The vast majority of studies undertaken on the effects of obesity on asthma are cross-sectional, or have only a short follow-up. Thus, the long-term effects of obesity on asthma remain completely unknown [4, 6]. Mostly, smokers and patients with other comorbidities have been excluded [4–7]. Early- and late-onset asthma have been regarded as different phenotypes with different prognoses [3, 11, 12], but in previous obesity-related studies the age of onset is often mixed. Effects of obesity on late-onset asthma have been evaluated only in one previous study with a cross-sectional setting [6]. In this study, obese patients with late-onset asthma were suggested to present features of more severe asthma compared to leaner patients [6].

No previous study has concentrated on evaluating long-term prognosis of adult patients, who are obese at diagnosis, being the aim of this study. We focused in evaluating the effects of diagnostic obesity on the use of oral corticosteroids (OCS) and respiratory-related hospital admissions at 12-year follow-up in patients diagnosed with adult-onset asthma.

Methods

Study patients

The Seinäjoki Adult Asthma Study (SAAS) is a 12-year follow-up study in which 257 patients were diagnosed with new-onset adult asthma between October 6, 1999 and April 17, 2002. >94% of the patients diagnosed with novel asthma in the study site were recruited to the study [13]. Asthma diagnosis was made by a respiratory specialist based on lung function measurements and typical symptoms of asthma. Asthma diagnosis requirements and inclusion and exclusion criteria have been published previously [13] (supplementary table S1). The exclusion criteria were a previous diagnosis of asthma at age <15 years and inability or unwillingness to sign the informed consent. Patients were not excluded due to smoking history, comorbidities or another lung disease. Patients were recruited from the diagnostic visit and after diagnosis the patients were treated in primary care, occupational healthcare, private healthcare or in specialised healthcare according to principles of the Finnish Asthma Programme [14]. The mean follow-up time was 12.2 years (range 10.8–13.9 years), after which 203 (79%) patients returned to a follow-up visit (between December 10, 2012 and October 31, 2013) (supplementary figure S1). Written informed consent was obtained to a study protocol approved by the ethics committee of Tampere University Hospital (Tampere, Finland) (R12122). The 12-year prognosis, smoking characteristics, comorbidities and clusters of the SAAS cohort have been published previously [9, 15–17].

Use of oral corticosteroids and hospitalisations

Self-reported OCS use was defined as affirmative answer to "Have you used cortisone tablets (prednisolone, prednisone, Medrol, Solomet, dexamethasone) as short courses due to your asthma?" Information on dispensed OCS was obtained from the Finnish Social Insurance Institution. Only dispensed OCS indicated for asthma were taken into account. More detailed information is included in the supplementary material. Hospitalisations were collected from medical records.

Anthropometric measures, lung function, asthma control and inflammatory parameters

Body mass index (BMI) was calculated from measured weight in kilograms and height in metres. Lung function was measured using a Vmax Encore 22 spirometer (Viasys Healthcare, Palm Springs, CA, USA) which was calibrated daily. Patients completed the structured questionnaire AQ20 (Airways Questionnaire 20) at the diagnostic and follow-up visits [18]. The Asthma Control Test (ACT) was completed at the follow-up visit. Asthma control was based on Global Initiative for Asthma 2010 report [19]. Further information is available in the supplementary material.

Statistical analyses

Continuous data are expressed as mean±SD or median (interquartile range). Comparisons between three groups were done by one-way ANOVA, Kruskal–Wallis test or Chi-squared test. Multivariable binary logistic regression analysis was performed to find out predictors for OCS use and hospitalisation. Forward and backward methods were used in choosing the final model. Independent variables were from diagnostic time-point and for OCS use included sex, age of asthma onset, respiratory symptoms <16 years, BMI, pre-bronchodilator forced expiratory volume in 1 s (FEV_1), smoking pack-years and blood eosinophils as categorised. For hospitalisations, independent variables were sex, age of asthma onset, COPD,

hypertension, BMI, pre-bronchodilator FEV_1 and AQ20 score as categorised. The final models contained no strong multicollinearity with r⩾0.7. To estimate interaction effects between BMI and blood eosinophil levels on OCS use, we constituted a stratified analysis in groups with high and low blood eosinophil levels with a test for interaction [20]. Statistical analyses were performed using IBM SPSS statistics software (versions 22 and 25; Armonk, NY, USA). A p-value <0.05 was regarded as statistically significant.

Results

Patient characteristics

The study population consisted of 203 patients with adult-onset asthma and their baseline and follow-up characteristics are shown in supplementary table S2. The patients were mostly female, overweight, with mean±SD age of asthma onset 46±14 years. Half of the patients had a history of smoking. At diagnosis, 92% were steroid-naïve; ICS therapy was started for all patients after diagnosis; and at 12-year follow-up 76% were daily ICS users.

Diagnostic obesity and use of OCS courses during the 12-year follow-up

The patients were divided into three groups according to their BMI at asthma diagnosis (normal weight <25 $kg{\cdot}m^{-2}$, overweight 25–29.99 $kg{\cdot}m^{-2}$, obese ⩾30 $kg{\cdot}m^{-2}$) (table 1). At the time of diagnosis, 24.1% were obese and 43.8% were overweight. After a mean follow-up time of 12.2 years, BMI was increased in all groups, with no difference in the weight gain between the groups (figure 1). Of the obese patients, 86% remained obese at the 12-year follow-up visit. At the long-term follow-up, most patients remained in their initial BMI group (figure 1). A comparison of asthma outcome between patients who remained obese and those who became non-obese until the 12-year follow-up visit is shown in supplementary table S3.

During the 12-year follow-up, patients who were obese at diagnosis reported more frequent use of OCS courses (figure 2a, table 2), were dispensed OCS more often (figure 2b, table 2) and at higher doses (figure 2c, table 2) compared to normal-weight patients. Of all patients, four (2.0%) reported daily use of OCS at the 12-year follow-up visit, but only two (1%) for asthma indication (table 2). During the whole follow-up period, 77% of all dispensed prednisolone (mg) was dispensed outside the pollen season. Of those reporting any OCS use during the follow-up period, three (4.6%) out of 65 had not purchased OCS and could be considered to have recall bias.

Considering use of other medication to treat asthma, obese patients were dispensed more ICS during the 12-year follow-up period than normal-weight or overweight patients (figure 2d). At the 12-year follow-up visit obese and overweight patients used add-on therapies (long-acting β_2-agonist, leukotriene receptor antagonist, theophylline or antimuscarinic agents) more often compared to normal-weight patients (table 1).

Diagnostic obesity and hospitalisations during 12-year follow-up

Proportion of patients having experienced any or unplanned respiratory-related hospitalisation during 12-year follow-up period was highest in the obese group (table 2, figure 3a and b). A similar finding was seen regarding total number of days in hospital (table 2, figure 3c).

Diagnostic obesity and other asthma outcomes

Patients who were obese at diagnosis more often had uncontrolled asthma at the 12-year follow-up visit and were more symptomatic at diagnosis and follow-up visit, as indicated by AQ20 and ACT scores compared to non-obese groups (tables 1 and 3). Blood neutrophils were higher and exhaled nitric oxide fraction (F_{eNO}) lower at 12-year follow-up in patients who were obese at diagnosis (table 3). FEV_1 and forced vital capacity were lower among obese patients at both diagnostic and follow-up visits (table 1). The number of comorbidities and number of medications used to treat comorbidities were significantly higher in the overweight and obese groups. Obese and overweight patients suffered more often from diabetes, hypertension and psychiatric diseases, while only obese patients more often had depression and treated dyspepsia compared to normal-weight patients (table 3). Airway hyperresponsiveness to histamine was evaluated for 62 (30.5%) patients at the time of diagnosis, but the provocative dose to cause a 15% fall in FEV_1 showed no statistically significant difference between the BMI groups (supplementary figure S2).

Diagnostic predictors for use of OCS to treat asthma

To investigate diagnostic predictors for self-reported OCS use at 12-year follow-up period we performed multivariate binary logistic regression analysis. Diagnostic predictors for OCS use were female sex, obesity and overweight, low blood eosinophil level before start of treatment (<$0.20\times10^9{\cdot}L^{-1}$), lower pre-bronchodilator FEV_1 (% predicted) at diagnosis and respiratory symptoms during childhood (table 4). Pack-years did not predict OCS use, and age of onset >60 years was a protective factor. Asthma–COPD overlap (ACO), diabetes, hypertension and coronary heart disease, smoking status and atopy at diagnosis were tested in the model, but did not predict OCS use. When using dispensing of one or more OCS as

TABLE 1 Basic demographics, medication and lung function at diagnosis and at 12-year follow-up visit in patients divided into three groups based on body mass index (BMI) at asthma diagnosis

	BMI <25 kg·m^{-2}		BMI 25–29.99 kg·m^{-2}		BMI ⩾30 kg·m^{-2}		p-value[#]	p-value[¶]
	Diagnosis	12-year follow-up visit	Diagnosis	12-year follow-up visit	Diagnosis	12-year follow-up visit		
Subjects	65		89		49			
Age years	40±13	53±13	49±13	61±13	48±13	60±13	<0.001	<0.001
Female	40 (61.5)		50 (56.2)		28 (57.1)		0.791	
BMI kg·m^{-2}	22.6±2.0	24.0±2.9	27.4±1.3	28.5±2.9	34.1±4.3	34.7±6.2	<0.001	<0.001
Waist circumference female >80 cm/male >94 cm	ND	36 (55.4)	ND	82 (94.3)	ND	48 (98.0)	ND	<0.001
Smoking history	32 (49.2)	35 (53.8)	43 (48.3)	44 (49.4)	28 (57.1)	28 (57.1)	0.585	0.670
Current smokers	11 (16.9)	8 (12.3)	14 (15.7)	16 (18.0)	11 (22.4)	6 (12.2)	0.837	0.525
Pack-years (current/ex-smokers)	8 (3–16)	10 (2–20)	10 (6–20)	18 (7–31)	16 (10–30)	20 (13–34)	0.048	0.011
Rhinitis	ND	49 (75.4)	ND	55 (61.8)	ND	38 (77.6)	ND	0.079
Atopic (skin-prick positive)[+]	29 (47.5)	ND	25 (30.9)	ND	14 (34.1)	ND	0.114	ND
Respiratory symptoms <16 years	ND	19 (29.7)	ND	18 (20.2)	ND	9 (18.8)	ND	0.286
Daily ICS users	3 (4.6)	46 (70.8)	13 (14.9)	67 (75.3)	0	42 (85.7)	0.004	0.169
Self-reported ICS dose of daily users in budesonide equivalents µg	ND	800 (400–1000)	ND	800 (400–1000)	ND	800 (788–1125)	ND	0.247
Add-on medication[§]	ND	26 (40)	ND	41 (46.1)	ND	36 (73.5)	ND	0.001
Pre-BD FEV_1 % predicted	81±18	87±15	82±19	86±20	76±14	81±16	0.018	0.017
Pre-BD FVC % predicted	92±15	100±12	90±18	99±15	83±13	90±17	0.010	0.001
Pre-BD FEV_1/FVC	0.74 (0.67–0.81)	0.73 (0.65–0.79)	0.76 (0.70–0.82)	0.74 (0.67–0.79)	0.76 (0.72–0.79)	0.74 (0.68–0.79)	0.651	0.691
Post-BD FEV_1/FVC	0.79 (0.73–0.86)	0.76 (0.69–0.80)	0.79 (0.75–0.83)	0.74 (0.69–0.81)	0.79 (0.73–0.82)	0.75 (0.70–0.80)	0.879	0.895
Annual change FEV_1 during follow-up[f] mL	ND	−43±37	ND	−52±36	ND	−48±36	ND	0.389
Blood eosinophils ×10^9·L^{-1}	0.30 (0.18–0.50)	0.17 (0.11–0.28)	0.21 (0.12–0.40)	0.16 (0.10–0.25)	0.22 (0.18–0.40)	0.18 (0.09–0.28)	0.505	0.763
Blood eosinophils ⩾0.20×10^9·L^{-1}	44 (74.6)	29 (44.6)	53 (62.4)	34 (38.2)	32 (66.7)	22 (44.9)	0.306	0.645
AQ20 score	6 (2–8)	3 (1–6)	6 (3–9)	3.5 (1–6)	8 (5–12)	7 (3.5–9)	0.007	<0.001

Data are presented as n, mean±SD, n (%) or median (interquartile range), unless otherwise stated. Means between the three BMI groups were compared by one-way ANOVA, medians by independent-samples Kruskal–Wallis test; comparisons were performed using Chi-squared test for categorical variables. BMI: body mass index; ICS: inhaled corticosteroid; BD: bronchodilator; FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; AQ20: Airways Questionnaire 20; ND: not determined. [#]: between BMI groups at diagnosis; [¶]: between BMI groups at 12-year follow-up visit; [+]: information on atopy available from 183 patients; [§]: includes any of the following in use: long-acting β_2-agonist, leukotriene receptor antagonist, theophylline and tiotropium; [f]: from maximal point of lung function within 2.5 years from diagnosis (and start of treatment) to 12-year follow-up visit.

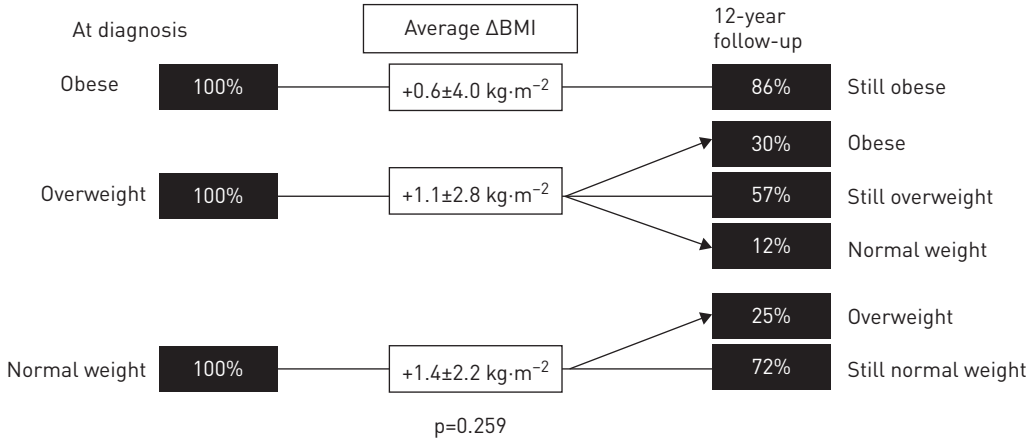

FIGURE 1 Diagnostic body mass index (BMI) groups and development of BMI during the 12-year follow-up period. ΔBMI presented as mean±SD; p-value assessed by one-way ANOVA. n=203 at diagnosis and follow-up.

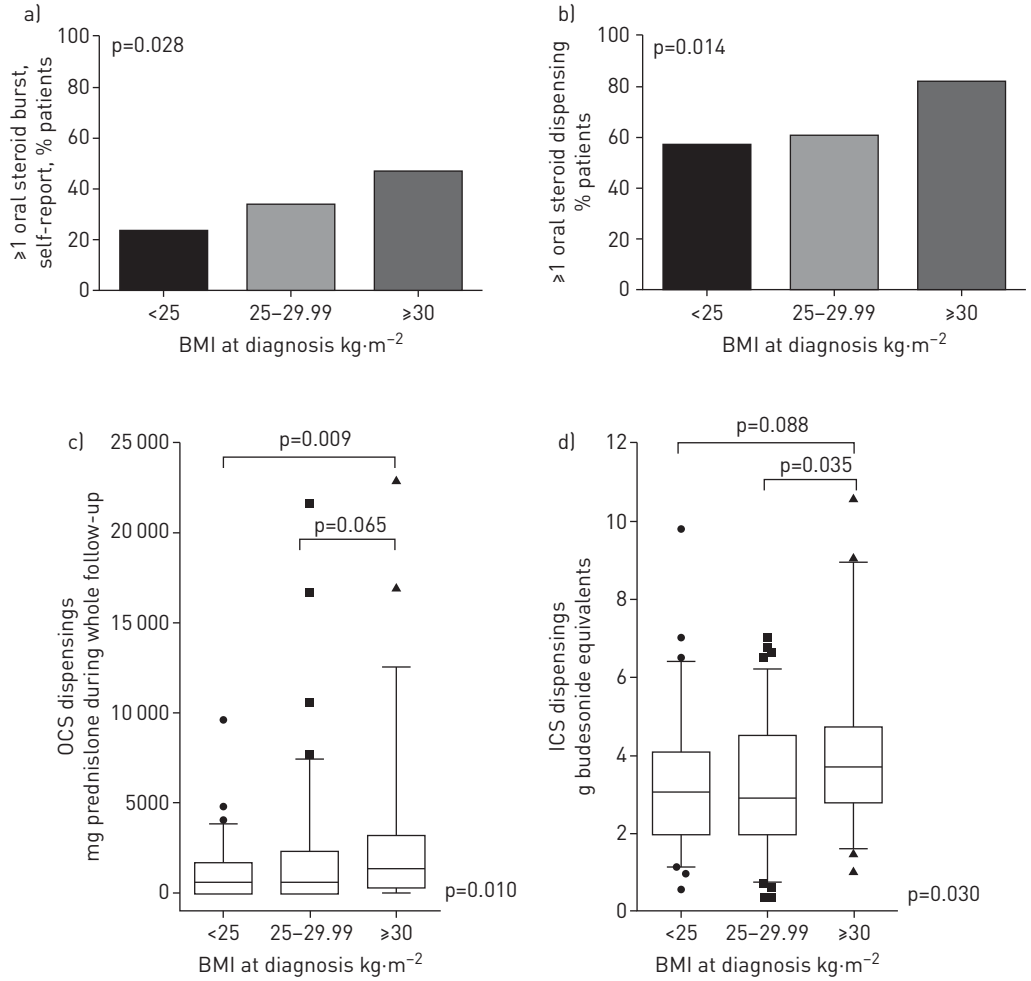

FIGURE 2 a) Self-reported and b, c) dispensed oral corticosteroids (OCS) and d) dispensed inhaled corticosteroids (ICS) during 12-year follow-up in patients divided according to body mass index (BMI) at the moment of asthma diagnosis. a, b) statistical comparison performed by Chi-squared test; c, d) data are presented as median, 25–75 percentiles and 5–95 percentiles; medians compared by Kruskal–Wallis test adjusted by Bonferroni correction for multiple tests.

TABLE 2 Use of oral corticosteroids (OCS) and hospitalisations during 12-year follow-up in patients divided according to body mass index (BMI) at the moment of asthma diagnosis

	BMI <25 kg·m^{-2}	BMI 25–29.99 kg·m^{-2}	BMI ⩾30 kg·m^{-2}	p-value
Subjects	65	89	49	
OCS				
Reported using ⩾1 OCS burst during follow-up	15 (23.1)	28 (33.7)	22 (46.9)	0.028
Reported daily use of OCS at 12-year follow-up visit	1 (1.5)	2 (2.2)	1 (2.0)	0.952
Dispensed ⩾1 package OCS during 12-year follow-up	37 (56.9)	54 (60.7)	40 (81.6)	0.014
Dispensed OCS during 12-year follow-up mg prednisolone	600 (0–1650)	520 (0–2305)	1350 (280–3180)	0.010
Dispensed OCS per year during 12-year follow-up mg prednisolone per year	45 (0–133)	42 (0–182)	122 (23–254)	0.009
Hospitalisations				
⩾1, all respiratory-related	11 (16.9)	24 (27.0)	19 (38.8)	0.033
⩾1, all respiratory-related unplanned	5 (7.7)	7 (7.9)	11 (22.4)	0.019
Hospital days, all respiratory-related n	1±3	4±12	5±10	0.029
Hospital days, all respiratory-related unplanned n	1±2	2±8	3±7	0.020

Data are presented as n, n (%), median (interquartile range) or mean±SD, unless otherwise stated. Means between BMI groups compared by one-way ANOVA with Tukey's post-test, medians by Kruskal–Wallis test adjusted by Bonferroni correction for multiple tests. Categorical variables compared by Chi-squared test with comparison of column proportions by z-test and adjusting p-values by Bonferroni method. In pairwise comparisons, in all variables (except ⩾1 hospitalisations, all respiratory-related unplanned) p<0.05 between BMI <25 kg·m^{-2} and BMI ⩾30 kg·m^{-2} groups. In unplanned hospitalisations and proportion of patients with purchased ⩾1 package oral steroid during 12-year follow-up, p<0.05 between BMI 25–29.99 kg·m^{-2} and BMI ⩾30 kg·m^{-2} groups.

dependent variable, female sex, diagnostic obesity and blood eosinophil level <0.20×10^9·L^{-1} before start of treatment were found as predictors (supplementary table S4).

To examine hypothesis that only obese patients with non-eosinophilic asthma at diagnosis are prone to exacerbations, we divided patients into low and high eosinophil groups (cut-point 0.20×10^9·L^{-1}) based on blood eosinophil level at diagnosis. In patients with low eosinophil level, higher proportion of obese (68.8%) and overweight (50.0%) had used at least one OCS course during follow-up compared to normal-weight patients (20.0%, p=0.023). In those with high blood eosinophils, the corresponding proportions were 37.5%, 22.5% and 20.5%, respectively (p=0.198) (supplementary table S5). p-values of interaction for overweight (p=0.081) and obesity (p=0.090) showed tendency towards interaction between obesity and low blood eosinophil level.

To further evaluate whether high or low blood eosinophil levels at diagnosis in obese patients result in different outcomes of asthma, we compared these groups. In addition to the increased OCS use, obese

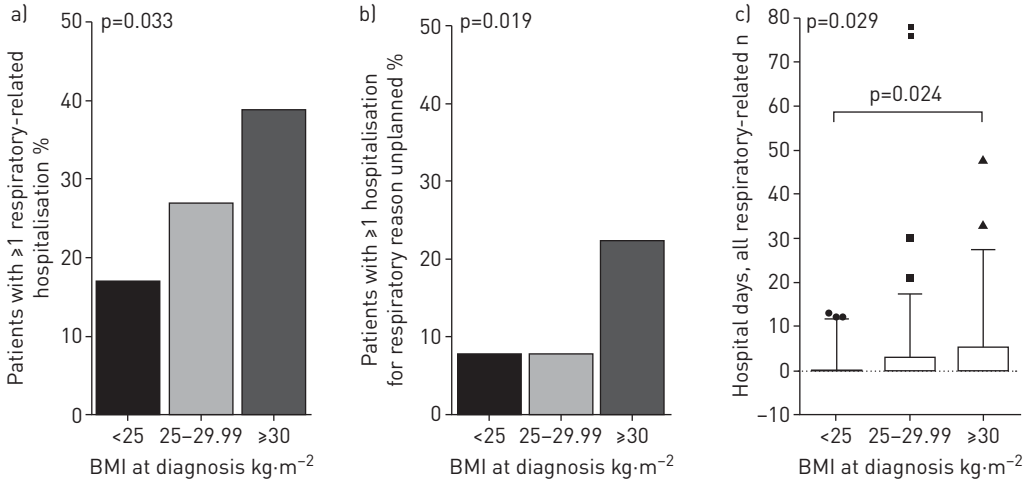

FIGURE 3 All a, c) respiratory-related and b) unplanned hospital admissions during 12-year follow-up in patients divided according to body mass index (BMI) at asthma diagnosis. a, b) statistical comparison performed by Chi-squared test; c) data are presented as median, 25–75 and 5–95 percentiles; medians compared by Kruskal–Wallis test adjusted by Bonferroni correction for multiple tests.

TABLE 3 Secondary asthma-related outcomes at 12-year follow-up visit in patients divided according to body mass index (BMI) at the moment of asthma diagnosis

	BMI <25 kg·m^{-2}	BMI 25–29.99 kg·m^{-2}	BMI ⩾30 kg·m^{-2}	p-value
Subjects	65	89	49	
Control, severity and symptoms				
Uncontrolled	17 (26.2)	17 (19.1)	26 (53.1)	0.001
ACT score	23 (20–25)	22 (20–24)	20 (16–22)	<0.001
Daily use of SABA	6 (9.2)	9 (10.1)	8 (16.3)	0.442
Severe asthma ERS/ATS[#]	1 (1.5)	5 (5.6)	6 (12.2)	0.056
Asthma severity, GINA[¶]				
Mild intermittent/mild persistent	19 (29.7)	27 (30.7)	6 (12.2)	0.001
Moderate persistent	42 (65.6)	50 (56.8)	28 (57.1)	
Severe persistent	3 (4.7)	11 (12.5)	15 (30.6)	
Adherence				
Average 12-year adherence to ICS[+] %	63 (40)	72 (37)	70 (38)	0.353
Asthma-related visits to healthcare during 12-year follow-up period				
All	14 (7–22.5)	14 (9–19.5)	17 (10.5–28.5)	0.192
Unplanned	3 (1–8.5)	4 (1–9)	3 (0.5–11)	0.772
Inflammatory parameters				
Total IgE kU·L^{-1}	69 (25–167)	56 (23–183)	61 (25–129)	0.818
F_{eNO} ppb	12 (6–28)	12 (6–19)	7 (5–15)	0.031
Blood eosinophils ×10^9·L^{-1}	0.17 (0.11–0.28)	0.16 (0.10–0.25)	0.18 (0.09–0.28)	0.763
Blood neutrophils ×10^9·L^{-1}	3.5 (2.5–4.6)	3.7 (3.0–4.9)	4.4 (3.2–4.9)	0.049
IL-6 pg·mL^{-1}	1.23 (0.86–2.07)	1.83 (1.23–2.82)	3.42 (1.75–5.24)	<0.001
hs-CRP mg·L^{-1}	0.57 (0.28–1.48)	1.31 (0.83–2.23)	2.58 (1.01–5.11)	<0.001
Comorbidities				
Number of comorbidities	0 (0–1)	1 (0–2)	2 (1–4)	<0.001
Number of other than asthma/allergy drugs	0 (0–2)	2 (0–4)	3 (2–7)	<0.001
Diabetes[§]	3 (4.6)	9 (10.1)	17 (34.7)	<0.001
Hypertension[§]	9 (13.8)	30 (33.7)	30 (61.2)	<0.001
Psychiatric[§]	2 (3.1)	14 (15.7)	11 (22.4)	0.007
Depression[§]	2 (3.1)	7 (7.9)	8 (16.3)	0.040
Treated dyspepsia/GORD[f]	0	7 (7.9)	9 (18.4)	0.002

Data are presented as n, n (%) or median (interquartile range), unless otherwise stated. Medians compared by Kruskal–Wallis test; categorical variables by Chi-squared test. ACT: Asthma Control Test; SABA: short-acting β_2 agonist; ERS: European Respiratory Society; ATS: American Thoracic Society; GINA: Global Initiative for Asthma; ICS: inhaled corticosteroids; F_{eNO}: exhaled nitric oxide fraction; IL: interleukin; hs-CRP: high-sensitivity C-reactive protein; GORD: gastro-oesophageal reflux disease. [#]: defined according to ERS/ATS 2014 criteria [21]; [¶]: defined by GINA 2002 guideline [22]; [+]: percentage of true dispensed ICS in µg per true prescribed daily ICS in µg per 12-year follow-up, information missing from 22 patients for whom regular ICS medication was not prescribed through the whole follow-up; [§]: based on self-report disease and medication data; [f]: based on medication use.

patients with low eosinophil levels tended to be older, have poorer FEV_1 and had lower high-sensitivity C-reactive protein (hsCRP) at 12-year follow-up compared to obese patients with higher eosinophil levels (supplementary table S6).

Diagnostic predictors for hospitalisation for respiratory reasons

Our next goal was to evaluate diagnostic predictors for respiratory-related hospitalisations. Predictors for one or more hospitalisations during the 12-year follow-up period were obesity, hypertension, ACO and AQ20 score ⩾12 (indicating very high symptoms) at diagnosis (table 5).

Discussion

In this study we examined prognosis of patients who were diagnosed with adult-onset asthma and who were obese at diagnosis. Of those patients, 86% were still obese 12 years after diagnosis. The patients who were obese at the time of diagnosis more often used OCS courses and were more likely to be hospitalised during the 12-year follow-up period compared to normal-weight patients. Considering that long-term studies have been lacking on the effects of obesity on asthma and age of asthma onset has rarely been considered in previous studies, our study gives important and unique perspective regarding long-term effects of obesity on adult-onset asthma.

TABLE 4 Diagnostic predictors for use of one or more oral corticosteroid (OCS) burst during 12-year follow-up

	OR (95% CI)	p-value
Female	3.25 (1.40–7.59)	0.006
BMI at diagnosis <25 kg·m^{-2} (ref)		
BMI at diagnosis 25–29.99 kg·m^{-2}	2.51 (1.03–6.15)	0.044
BMI at diagnosis ⩾30 kg·m^{-2}	4.15 (1.54–11.19)	0.005
Age of onset <45 years (ref)		
Age of onset 45–60 years	0.92 (0.42–2.02)	0.841
Age of onset >60 years	0.22 (0.06–0.82)	0.024
Pack-years at diagnosis ⩾10	1.44 (0.59–3.50)	0.422
Blood eosinophils at diagnosis <0.20×10^{9}·L^{-1}	3.70 (1.71–8.03)	0.001
Pre-BD FEV_1 at diagnosis >80% predicted (ref)		
Pre-BD FEV_1 at diagnosis 60–80% predicted	2.45 (1.05–5.73)	0.039
Pre-BD FEV_1 at diagnosis <60% predicted	4.89 (1.45–16.48)	0.011
Asthma symptoms <16 years	3.07 (1.13–6.30)	0.025

BMI: body mass index; BD: bronchodilator; FEV_1: forced expiratory volume in 1 s. n=186 due to missing data. Odds ratio values obtained from multivariable binary logistic regression analysis. For BMI 25–29.99 kg·m^{-2} and BMI ⩾30 kg·m^{-2} at diagnosis, unadjusted ORs 1.70 (95% CI 0.82–3.50) and 2.95 (95% CI 1.32–6.59), respectively. Treated dyspepsia/gastro-oesophageal reflux disease was not found as an independent determinant associated with OCS use (unadjusted OR 1.61 (95% CI 0.57–4.52), adjusted OR 0.90 (95% CI 0.25–3.23)) and after adding it to the model, overweight and obesity were still significant predictors for oral steroid use (OR 2.52 (95% CI 1.03–6.18) and OR 4.25 (95% CI 1.51–11.94), respectively).

In previous studies, obesity has been associated with incident asthma [1, 2]. However, information has been conflicting regarding effects of obesity on asthma outcomes such as asthma control, and longitudinal studies have been lacking [4, 7, 23]. Furthermore, we found no studies assessing long-term prognosis for an obese patient with new asthma or long-term effects of obesity on adult/late-onset asthma. Therefore, our study has a unique setting. In our study almost nine out of 10 obese patients at diagnosis were still obese 12 years after diagnosis, the proportion being closely similar to that found in general population [24, 25]. Based on our material of limited size, migration between BMI categories in patients with asthma seems roughly similar or shows slightly more progression towards obesity compared to the general population [24, 25]. Of those who were obese at diagnosis, 47% reported use of at least one OCS course due to asthma during the following 12 years and 82% had purchased OCS, both 1.4- to two-fold compared to patients who were normal weight at diagnosis, and the results remained after adjustments (OR 4.15 for obese *versus* normal-weight; table 4). Furthermore, median dose of prednisolone dispensed over the

TABLE 5 Diagnostic predictors for at least one hospitalisation during 12-year follow-up

	OR (95% CI)	p-value
Female	1.15 (0.56–2.40)	0.700
BMI at diagnosis <25 kg·m^{-2} (ref)		
BMI at diagnosis 25–29.99 kg·m^{-2}	2.34 (0.96–5.71)	0.062
BMI at diagnosis ⩾30 kg·m^{-2}	2.78 (1.03–7.54)	0.045
Age of onset ⩾40 years	0.53 (0.24–1.18)	0.119
Hypertension at diagnosis	2.81 (1.10–7.17)	0.031
ACO at diagnosis	4.30 (1.10–16.91)	0.037
Pre-BD FEV_1 at diagnosis >80% predicted (ref)		
Pre-BD FEV_1 at diagnosis 60–80% predicted	0.67 (0.29–1.56)	0.352
Pre-BD FEV_1 at diagnosis <60% predicted	1.40 (0.44–4.44)	0.565
AQ20 symptom score ⩾12	3.08 (1.25–7.60)	0.015

BMI: body mass index; ACO: asthma–COPD overlap; BD: bronchodilator; FEV_1: forced expiratory volume in 1 s; AQ20: Airways Questionnaire 20. n=191 due to missing data. Odds ratio values obtained from multivariable binary logistic regression analysis. For BMI 25–29.99 kg·m^{-2} and BMI ⩾30 kg·m^{-2} at diagnosis, unadjusted ORs 1.81 (95% CI 0.82–4.03) and 3.11 (95% CI 1.31–7.39), respectively. Poor inhaled corticosteroid adherence (<80%) (calculated as average adherence for the whole 12-year follow-up) was tested to the model, but no association with hospitalisations was found.

follow-up period in obese patients was more than twice that in normal-weight patients. Poor use of controller treatment is not likely to explain the increased risk of exacerbations, because obese patients had purchased more ICS during the follow-up period than normal-weight patients. Proportion of OCS users differed in self-report *versus* dispensed data (47% *versus* 82%), which may be due to recall bias or purchasing OCS for reserve. However, because diagnostic obesity was associated with self-reported OCS use as well as with dispensed OCS in adjusted analysis, recall bias is unlikely to be playing a significant role in our main result. No similar studies with long-term follow-up in patients with confirmed diagnosis of asthma were found, but in previous short follow-up studies based on electronic records [26, 27], obesity at baseline year (not diagnosis) in patients with asthma was reported as a risk factor for two or more asthma attacks (OR 1.27) [26] or for at least one OCS dispensing linked to asthma encounter (OR 1.36) [27] in the following 1–2 years. In our self-report based data, overweight was a risk factor for increased OCS use, being supported by the previous studies [26, 27]. In total, our results add to previous ones by showing that being overweight or obese at diagnosis and remaining so in the long term is a significant risk factor for exacerbations in patients with confirmed diagnosis of adult-onset asthma.

Only one cross-sectional study [6] has assessed OCS use in early- and late-onset phenotypes of obese asthma and found that only obese subjects with early-onset, but not late-onset asthma, had more asthma exacerbations requiring OCS than non-obese subjects in the corresponding age of onset category. The patient materials in our study and the previous Severe Asthma Research Program (SARP) study differ in many ways: by setting (longitudinal *versus* cross-sectional), definition of late-onset asthma (SAAS $\geqslant$15 years, SARP $\geqslant$12 years), patient selection (unselected *versus* exclusion of smokers), proportion of severe asthma (5.6% *versus* 26%) and average age of asthma onset (46 years *versus* 27 years) [6]. Therefore, our studies may contain partly different phenotypes of asthma, which may explain the inconsistency in the results.

Respiratory-related hospitalisation was another important end-point of this study that was found to be twice as common in patients with asthma who were obese at diagnosis compared to leaner patients. Previous studies with similar setting were not found, but in study based on electronic records, obese and overweight patients with asthma had larger risk for asthma-related emergency room visits or hospitalisation (OR 1.40 for both) [27]. In our study, COPD and hypertension comorbidities were additional risk factors for respiratory-related hospitalisation. In a Taiwanese population-based study, patients with ACO according to diagnostic codes experienced more respiratory-related hospital visits than patients with asthma, supporting our results [28], but we could not find previous studies on hypertension as a risk factor for respiratory-related hospitalisations, constituting a new finding.

What are the plausible mechanisms behind obesity-related worsening of asthma, and what is the role of inflammation? Obesity has been associated with reduced corticosteroid responsiveness [29, 30] and non-eosinophilic asthma [31]. In our study, blood eosinophil levels were similar between diagnostic BMI groups, but our results suggest that the most plausible OCS users were those who were both obese and had low blood eosinophil level at diagnosis ($<0.20\times10^{9}\cdot L^{-1}$), in a steroid-naïve situation. This implies that non-eosinophilic asthma and related reduced corticosteroid responsiveness [32] are important factors leading to exacerbations in obese patients. Besides OCS use, we noted only a few differences in long-term asthma outcome between obese patients with eosinophilic or non-eosinophilic asthma at diagnosis. However, it should be noted that our sample size was relatively low in the stratified analysis and the results should be confirmed in larger patient populations. According to our regression model, diagnostic low blood eosinophil level as such (suggesting non-eosinophilic asthma) predisposed for future OCS use. This is also a novel finding, given that previous studies have concentrated on predicting role of blood eosinophils in the ICS-treated situation. Overall, we show preliminary evidence that obese patients with new asthma and low blood eosinophil levels are the ones at highest risk for exacerbations and these patients need more careful follow-up and more effective interventions.

In addition, obesity has been proposed to worsen asthma control by affecting pulmonary mechanics, production of adipokines (*e.g.* leptin) and pro-inflammatory cytokines (*e.g.* interleukin (IL)-6, tumour necrosis factor-α) by adipose tissue and systemic inflammation [33], and *via* comorbidities such as depression [34] and gastro-oesophageal reflux disease [35]. Our cohort is predominantly female and on average middle-aged at asthma onset; in this and other previous studies female sex increased risk of exacerbations [26, 36]. Therefore, female sex hormones and menopause could play a role in worse outcome of asthma. Menopause has been associated with increased risk of asthma and respiratory symptoms [37, 38], the effect being stronger in those with higher BMI [38]. In our study, blood neutrophil level, IL-6 and hsCRP were higher in obese patients at 12-year follow-up, proposing a role for neutrophilic and systemic inflammation in obese asthma as previously suggested [39, 40], even though we cannot exclude the possible role of high corticosteroid use in provoking neutrophilic inflammation. In addition, lower F_{eNO} levels in our obese patients indicates a lesser role for type 2 T-helper mechanisms in obese,

late-onset asthma. Thus, our results suggest the concept of obese asthma involving non-type 2 mechanisms such as neutrophilia and systemic inflammation.

Our findings suggest that OCS use is more likely in patients with low FEV_1 at diagnosis before the start of treatment. This finding is unique, since previous studies have concentrated on the predictive role of lung function in the treated situation [26, 41]. Two previous studies support the significance of better baseline FEV_1 (<12 months from diagnosis) in predicting better asthma outcome: remission [42] and better control [15] of adult-onset asthma. We found no studies with exacerbations as an end-point. In our model, childhood respiratory symptoms were found to predict OCS use, but this was not repeated when dependent variable was dispensed OCS, leaving the finding unclear.

The major strengths of this study are the use of an unselected population with confirmed diagnosis of adult-onset asthma representing true adult asthma patients in clinics and a long follow-up period, considering that previous long-term follow-up studies on the effects of obesity have been lacking. Moreover, the two parameters of OCS used, self-reported and true dispensed, made the results more reliable. As limitation, BMI was used as measure of obesity, even though it does not describe the distribution of body fat. However, BMI has been used in the majority of asthma studies, making the results more comparable. Changing of BMI at long-term may affect the results, even though there was no statistically significant difference in the weight gain between the diagnostic BMI groups. Our results can be applied to a situation where an obese patient is encountered at diagnosis and obesity continues: what will be the prognosis for asthma? The results would be different if the obese group had lost weight and become normal-weight during the follow-up. Therefore, it is important to interpret the results in the light of long-term obesity.

Our results indicate that weight loss and weight control are important goals for obese patients with asthma. In support of this, in a large population-based database study the risk for emergency department visit or hospitalisation due to exacerbation decreased by half in a 2-year follow-up after bariatric surgery in obese asthma patients [6, 43]. Furthermore, previous results suggest that exacerbations can be reduced by a supervised weight reduction programme and low-energy diet for 8 weeks, which resulted in an average weight loss of 11.3% after 1 year [44]. However, more studies should be undertaken with exacerbations as an end-point. Overall, weight loss of 5–10% by lifestyle intervention has improved symptom control and quality of life in obese asthmatics [33, 45], but whether 5–10% weight loss is enough to reduce exacerbations in the long term remains unclear.

Our study, for the first time, produced long-term data on the effects of obesity on asthma. We showed that, without intervention, obese patients with new adult-onset asthma often remain obese. They have more exacerbations and hospital admissions, despite having been dispensed ICS in addition in higher amounts in the long term. This is a patient group with a poor outcome of asthma and a high burden to healthcare. In addition, our study suggests that low diagnostic blood eosinophil level may be used to identify obese patients with the highest exacerbation risk. As current treatments are less effective in obese patients, and as weight loss has many beneficial effects, weight loss should be prioritised in the management of asthma in obese patients.

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