

Comorbidities in Difficult-to-Control Asthma



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What is already known about this topic? Comorbidities are associated with difficult-to-control asthma, but the prevalence and nature of comorbidities in patients with difficult-to-control asthma are unknown. Also, it is unclear which patients are most at risk of comorbidities.

What does this study add to our knowledge? This Dutch pharmacy database study shows that the majority of patients with difficult-to-control asthma have at least 2 comorbidities, and that asthmatic women of older age, former smokers, and prednisone-dependent asthmatics are at greatest risk of comorbidities.

How does this study impact current management guidelines? Patients with difficult-to-control asthma, in particular older women, former smokers, and prednisone-dependent patients, should be thoroughly screened, monitored, and, if necessary, treated for comorbidities.

BACKGROUND: Difficult-to-control asthma is associated with significant medical and financial burden. Comorbidities are known to contribute to uncontrolled asthma. Better insight into the prevalence, nature, and risk factors of comorbidities may optimize treatment strategies in patients with difficult-to-control asthma and decrease disease burden.

OBJECTIVES: The objectives of this study were to assess the prevalence, number, and type of comorbidities in difficult-to-control asthma compared with not-difficult-to-control asthma, and to investigate whether specific patient characteristics are associated with particular comorbidities.

METHODS: A total of 5,002 adult patients with a prescription for high-dose (>1,000 µg) fluticasone or oral corticosteroids, extracted from 65 Dutch pharmacy databases, were sent questionnaires about patient characteristics. Of the 2,312 patients who returned the questionnaires, 914 were diagnosed with difficult-to-control asthma. Diagnoses of comorbidities (gastroesophageal reflux, nasal polyps, cardiovascular disease, anxiety/depression, obesity, and diabetes) were based on treatment

prescriptions or questionnaires. Associations were assessed using multivariable logistic regression analyses.

RESULTS: A total of 92% of patients with difficult-to-control asthma had ≥1 comorbidity. Patients with difficult-to-control asthma had more comorbidities (mean ± SD comorbidities 2.22 ± 1.27 vs 1.69 ± 1.32; $P < .01$), and a significantly higher prevalence of each comorbidity, compared with patients with not-difficult-to-control asthma, except for diabetes and nasal polyposis. Comorbidities were associated with specific patient characteristics, including older age, female gender, smoking history, and chronic prednisone use.

CONCLUSIONS: Almost all patients with difficult-to-control asthma have comorbidities, in particular asthmatic women of older age, former smokers, and asthmatics who are prednisone dependent. Recognition of these typical characteristics can help physicians in the diagnostic workup, so that adequate preventive measures can be taken. © 2017 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2018;6:108-13)

Key words: Asthma; Difficult-to-control asthma; Comorbidity; Prevalence; Uncontrolled asthma

Difficult-to-control asthma is defined as uncontrolled asthma despite treatment with high-dose inhaled corticosteroids (ICS) or chronic systemic corticosteroids, and is characterized by everyday asthma symptoms, frequent exacerbations, and/or hospitalizations.^{1,2} A substantial proportion of the adult asthma population suffers from difficult-to-control asthma,³ which is problematic because uncontrolled disease leads to significant medical and financial burden.⁴⁻⁸

Many factors are known to be associated with uncontrolled asthma including poor adherence to treatment, inadequate inhalation technique, socioeconomic and psychological factors, environmental exposures, and smoking.⁹⁻¹¹ Also comorbidities such as gastroesophageal reflux,^{12,13} obesity,¹⁴⁻¹⁶ and psychiatric disorders^{17,18} have been shown to be associated with

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Abbreviations used

ACO- Asthma COPD overlap
ATS- American Thoracic Society
COPD- Chronic obstructive pulmonary disease
ERS- European Respiratory Society
ICS- Inhaled corticosteroids
LABA- Long-acting β_2 -agonist
OCS- Oral corticosteroids
PY- Pack years

difficult-to-control asthma, and managing these comorbidities may improve asthma control.^{11,19} Better insight into the prevalence and nature of comorbidities, and early identification of patients at risk may help to optimize diagnostic, preventive, and management strategies for patients with difficult-to-control asthma. However, only few studies have investigated the prevalence of comorbidities in these patients,^{11,19,20} and none of these studies have explored risk factors or patient characteristics associated with these comorbidities.

In the present study, we hypothesized first that patients with uncontrolled asthma have a higher number of comorbidities than those with controlled asthma, second, that not all comorbidities are associated with uncontrolled asthma, and third, that specific patient characteristics are associated with comorbidities that have impact on asthma control. To test these hypotheses we used questionnaires and prescription data from 1,571 patients with controlled and uncontrolled asthma despite high-dose ICS and bronchodilator treatment.

METHODS

Patients

Adults (≥ 18 years) with asthma and a prescription for high-intensity asthma treatment were selected from a Dutch pharmacy database. High-intensity treatment was defined as $\geq 1,000$ $\mu\text{g/d}$ fluticasone equivalent plus a long-acting β_2 -agonist (LABA), or 500-1,000 $\mu\text{g/d}$ fluticasone equivalent plus chronic oral corticosteroids (OCS) (≥ 6 months, ≥ 5 mg/d prednisone equivalent) plus LABA. Questionnaires were sent by regular mail to all patients ($n = 5,002$), of which 2,312 (46.2%) were returned and analyzed. Questionnaires contained questions on demographics (gender, age, height, weight), asthma symptoms, airborne allergies (house dust mite, cat dander, dog dander, mixed grass pollens, mixed tree pollens, mixed fungi), smoking, childhood asthma, and treatment for nasal polyposis. Responses to these questions were used to identify patients with asthma. Asthma diagnosis was based on physician diagnosed "asthma" or "chronic obstructive pulmonary disease (COPD)" with no or limited smoking history (<10 pack years [PY]). If smoking history was ≥ 10 PY, asthma diagnosis was based on a history of childhood asthma and/or presence of allergic symptoms and/or treatment for nasal polyposis (Figure 1).

Definition of difficult-to-control asthma and not-difficult-to-control asthma

A diagnosis of difficult-to-control asthma was based on the recent European Respiratory Society/American Thoracic Society (ERS/ATS) severe asthma guidelines, which distinguishes between severe asthma and difficult-to-control asthma.² Patients had to fulfill at least one of the following criteria: (1) Asthma Control Questionnaire ≥ 1.5 ,²¹ (2) >2 exacerbations in the previous year for which a course of OCS was needed, (3) ≥ 1 hospitalization

because of asthma in the previous year, and/or (4) chronic treatment with OCS. Patients not fulfilling one of these criteria were labeled as having not-difficult-to-control asthma (Figure 1).

Assessment of comorbidities

The diagnosis of comorbidities was based on at least one prescription for medications for the following: (1) anxiety/depression; (2) cardiovascular disease; (3) diabetes; (4) gastroesophageal reflux. Obesity (5) was defined as body mass index ≥ 30 kg/m^2 and was calculated from self-reported weight. Data on height and nasal polyposis were retrieved from the questionnaires. A diagnosis of nasal polyposis was based on a self-reported doctor diagnosis or previous surgery for nasal polyps.

Analysis

Group characteristics were described as proportions, mean \pm standard deviation for normally distributed variables, or median (interquartile range) for non-normally distributed variables. Proportions of the total number of comorbidities and of each type of comorbidity were calculated and compared between patients with difficult-to-control and not-difficult-to-control asthma. Student *t*-tests, Mann-Whitney *U* tests, and χ^2 tests were used to compare patient characteristics, based on distribution of data, as appropriate. Multivariable logistic regression models were applied to investigate independent risk factors for the presence of particular types of comorbidities. The following patient characteristics were entered into the models: (1) age, (2) gender, (3) PY of smoked cigarettes, (4) childhood asthma, (5) allergic symptoms, (6) ICS dose, and (7) chronic use of OCS. Characteristics with *P* values of $<.05$ were considered significantly different between the groups or associated with comorbidities. All analyses were performed with SPSS 22.0 (IBM Corporation, Armonk, NY). The study was approved by the hospital medical ethics board (MEC W11-064; NTR no. 3546).

RESULTS

Of the 2,312 patients who returned the questionnaires, 1,571 (67.9%) had asthma and were on high-intensity treatment. Of these, 914 (58.2%) had difficult-to-control asthma and 657 (41.8%) not-difficult-to-control asthma (Figure 1). Patients with difficult-to-control asthma were older (65.0 ± 13.8 y vs 61.5 ± 15.5 y; $P < .01$) and had a more extensive smoking history (22.5 (9.6-39.0) PY vs 16.5 (6.4-31.0) PY; $P < .01$) as compared with patients with not-difficult-to-control asthma (Table 1).

Prevalence of comorbidities in difficult-to-control and controlled asthma

Patients with difficult-to-control asthma had more comorbidities than patients with not-difficult-to-control asthma (2.22 ± 1.27 vs 1.69 ± 1.32 ; $P < .01$). Figure 2 shows that the majority of patients with difficult-to-control asthma had at least one comorbidity (92.3%) that was lower (78.0%) in not-difficult-to-control asthma ($P < .01$). Diabetes was least prevalent in both groups (12.5% and 11.1%, respectively), followed by obesity (18.6% and 13.9%), nasal polyps (24.4% and 21.9%), and anxiety/depression (36.1% and 24.7%). More than half of the patients with difficult-to-control asthma had cardiovascular disease (63.8%) and gastroesophageal reflux (66.8%), whereas in patients with not-difficult-to-control asthma, these figures were 52.5% and 45.4%, respectively. All

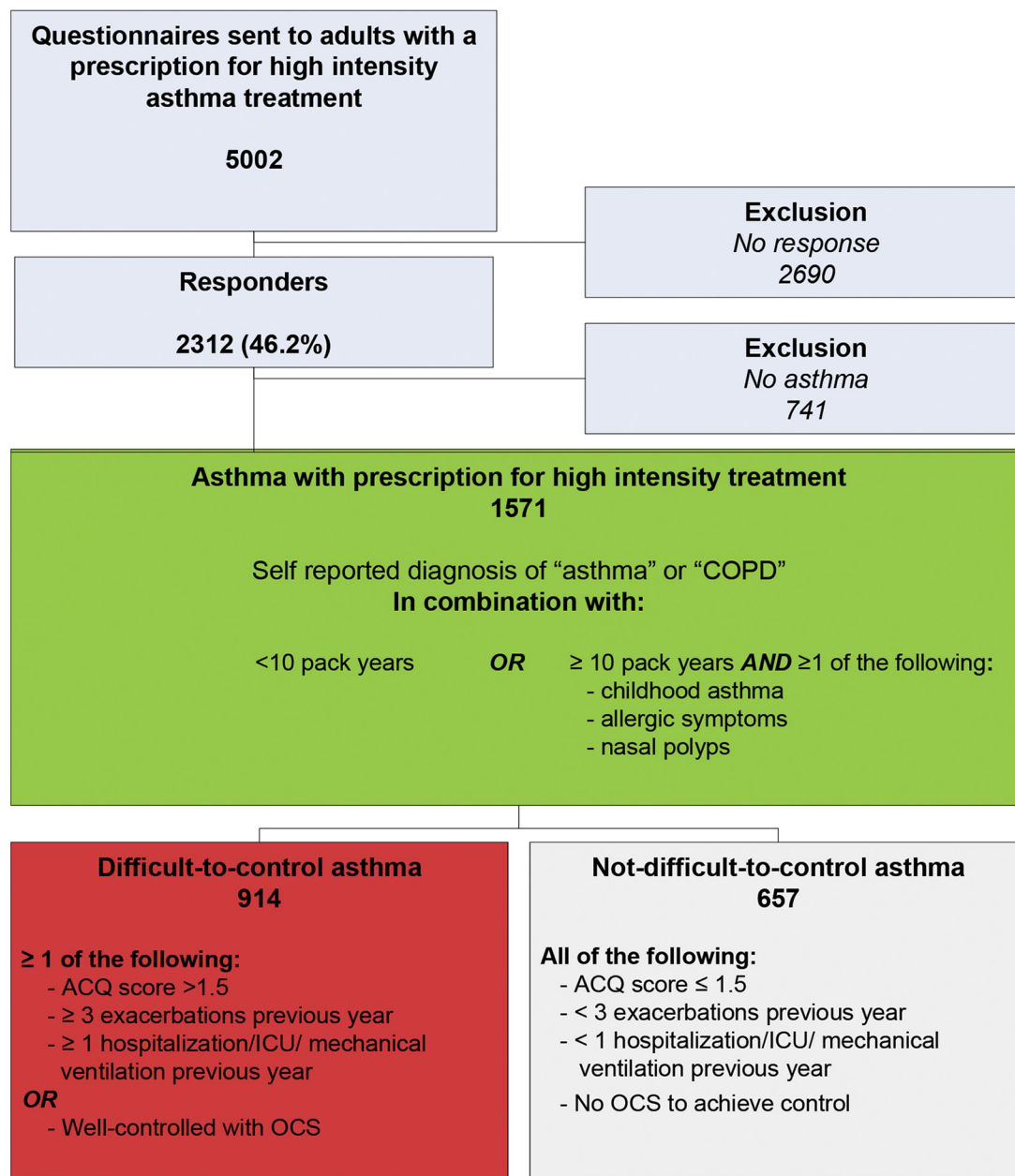


FIGURE 1. Flowchart of the design of the study. *ACQ*, Asthma Control Questionnaire; *COPD*, chronic obstructive pulmonary disease; *ICU*, intensive care unit; *OCS*, oral corticosteroids.

comorbidities, except for diabetes and nasal polyps, were significantly more prevalent in patients with difficult-to-control asthma as compared with those with not-difficult-to-control asthma (Figure 3).

Patient characteristics associated with comorbidities

Each of the comorbidities with a significantly higher prevalence in patients with difficult-to-control asthma was associated with a specific set of patient characteristics (Table II). Chronic prednisone use, female gender, and older age were independent risk factors for gastroesophageal reflux; older age and higher number of PY of cigarettes smoked were risk factors for cardiovascular disease; female gender, older age, and higher number of PY of cigarettes smoked were risk factors for

anxiety/depression; and female gender was a risk factor for obesity.

Other factors in the multivariable regression model (ICS dose, childhood asthma, and allergic symptoms) were not independently associated with the presence of any of the comorbidities.

DISCUSSION

This study shows that the majority (92%) of patients with difficult-to-control asthma have one or more comorbidities. Furthermore, patients with difficult-to-control asthma have more often multiple comorbidities than patients with not-difficult-to-control asthma. Cardiovascular disease, gastroesophageal reflux, anxiety/depression, and obesity are significantly more

TABLE 1. Patient characteristics of difficult-to-control and not-difficult-to-control asthma on high-intensity asthma treatment

	Difficult-to-control asthma	Not-difficult-to-control asthma	P value
N	914	657	
Age (y)*	65.0 ± 13.8	61.5 ± 15.5	<.01
Gender: Female	57.1%	58.20%	.67
BMI (kg/m ²)*	27.5 ± 6.3	26.9 ± 5.1	.10
Smoking status			<.01
Current	18.1%	14.5%	
Ex-smoker	44.5%	36.6%	
Never smoker	37.5%	48.8%	
Pack years (within (ex)smokers)†	22.5 (9.6-39.0)	16.5 (6.4-31.0)	<.01
Airway disease during childhood: Yes	49.6%	46.5%	.23
Nasal polyps: Yes	24.4%	21.9%	.24
Allergic symptoms: Yes	63.3%	65.1%	.47
ICS dose			<.01
500-1000 µg fluticasone equivalent	43.1%	32.1%	
>1000 µg fluticasone equivalent	56.9%	67.9%	
Chronic prednisone dose (mg/d)†	5.3 (3.4-8.7)	NA	
Number of comorbidities*	2.22 ± 1.27	1.69 ± 1.32	<.01

BMI, Body mass index; ICS, inhaled corticosteroids.

Bold indicates statistical significance ($P < .05$).

*Mean ± SD.

†Median (interquartile range).

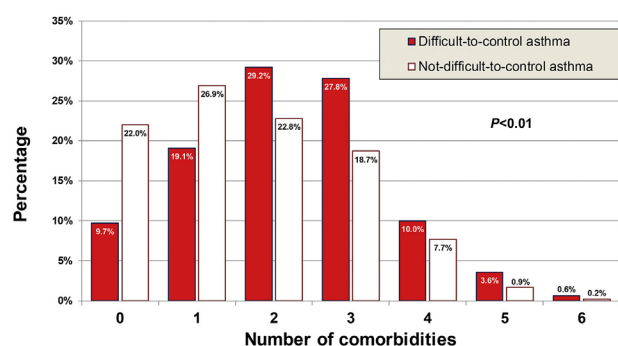


FIGURE 2. Prevalence of the presence of multiple comorbidities in difficult-to-control asthma and not-difficult-to-control asthma.

prevalent in patients with difficult-to-control asthma. Each of these comorbidities is associated with specific patient characteristics, of which higher age, female gender, positive smoking history, and chronic prednisone use are the most important. These results emphasize the important impact of comorbidities on asthma control, and provide a clinical profile of patients at highest risk of aggravating comorbidities.

The results of this study add important data to the existing literature, by identifying a clinical profile of patients at risk of comorbidities who are associated with uncontrolled asthma. The prevalences of comorbidities in patients with difficult-to-control asthma in our study are in line with those reported in the Belgian Severe Asthma Registry for anxiety/depression (around 30%), but not for obesity (47% vs 17.8% in our study), which might be explained by differences in life style factors (diet and exercise) between the Belgian and Dutch population. This study also showed a lower prevalence of gastroesophageal reflux (39% vs 62%),²² and also other cohort studies in severe or

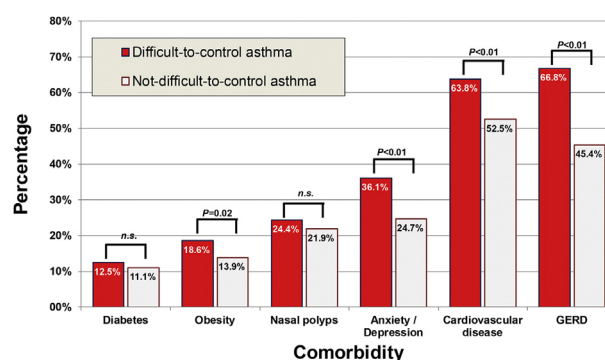


FIGURE 3. Prevalence per comorbidity in difficult-to-control asthma and not-difficult-to-control asthma. GERD, Gastroesophageal reflux disease.

difficult-to-control asthma found varying prevalences of between 30% and 64%.²³⁻²⁶ This wide variation in prevalences is probably due to differences in how this comorbidity was diagnosed (prescription-based in our study vs doctor's diagnosed in other studies). With respect to diabetes, the prevalences were comparable (10%) with the ones in our study.^{9,24,27}

Associations between specific patient characteristics and comorbidities have not been reported before. This study shows that higher age, female gender, smoking history, and chronic prednisone use were the most important factors associated with specific comorbidities. Remarkably, apart from older age, a positive smoking history was the only independent risk factor for cardiovascular disease, whereas female gender was associated with anxiety/depression, obesity, and gastroesophageal reflux. Smoking has been identified as a risk factor for cardiovascular disease in mild-moderate asthma previously.²⁸ Not

TABLE II. Patient characteristics that are independently associated with comorbidities in difficult-to-control asthma

	Gastro-esophageal reflux			Cardiovascular disease			Anxiety/depression			Obesity		
	OR	95% CI	P value	OR	95% CI	P value	OR	95% CI	P value	OR	95% CI	P value
Age*	1.33	1.23-1.44	<.01	2.16	1.95-2.39	<.01	1.15	1.05-1.24	<.01	0.99	0.90-1.09	.82
Gender: Female	1.59	1.28-1.99	<.01	1.22	0.96-1.55	.11	2.26	1.78-2.87	<.01	1.73	1.29-2.32	<.01
Pack years*	1.06	1.01-1.12	.34	1.12	1.05-1.19	<.01	1.10	1.04-1.17	<.01	1.06	0.99-1.13	.09
Childhood airway disease: Yes	1.07	0.86-1.33	.54	1.09	0.86-1.37	.50	1.26	0.99-1.58	.05	1.19	0.90-1.58	.22
Allergic symptoms: Yes	1.06	0.85-1.33	.60	1.12	0.88-1.43	.36	0.96	0.76-1.21	.71	0.87	0.61-1.25	.44
ICS dose	0.98	0.95-1.01	.21	1.01	0.98-1.05	.54	0.99	0.96-1.03	.59	0.98	0.94-1.02	.40
Chronic Prednisone: Yes	2.89	1.99-4.19	<.01	0.89	0.63-1.26	.52	1.38	0.96-1.90	.05	0.94	0.62-1.44	.78

CI, Confidence interval; ICS, inhaled corticosteroids; OR, odds ratio; Prednisone, use of systemic oral corticosteroids.

Bold indicates statistical significance ($P < .05$).

*Age and pack years are shown as effect per 10 y.

surprisingly, chronic prednisone use was associated with gastroesophageal reflux, which is a well-known adverse effect of this treatment.

One of the strengths of our study is the large representative sample of the general Dutch population. The pharmacy database used for this study represents 3.0% of the Dutch population that comes down to around 500,500 inhabitants. Furthermore, in the Netherlands, around 90% of the Dutch population collects medication from one single community pharmacy, which ensures the completeness of the analyzed dispensing records.²⁹ Finally, we used the ERS/ATS guideline definition of difficult-to-control asthma that includes intensity of anti-inflammatory treatment, allowing the identification of adequately matched control subjects.²

Our study also has limitations. First, we based the diagnoses of comorbidities on treatment prescriptions and questionnaires. This may have led to an under- or overestimation of the figures, in particular because the percentage of returned questionnaires was relatively low. The same holds true for prednisone, which might have been prescribed for a nonpulmonary diagnosis. However, it is very likely that patients on high-dose ICS used prednisone for their respiratory disease. Furthermore, we diagnosed patients with asthma based on dose of prescribed inhaled medication in combination with a medical history of childhood asthma, nasal polyps, or allergic symptoms, irrespective of smoking history. In doing so, we may have included patients with the so-called asthma COPD overlap (ACO).^{30,31} However, we believe that it is important to include current and ex-smokers, because smoking has been shown to be an important causative factor of uncontrolled asthma.³² Our data indeed show that smoking and older age are risk factors for comorbidities such as gastroesophageal reflux and cardiovascular disease. This could explain why patients with ACO have more exacerbations, are more frequently hospitalized, and thus are more difficult-to-control than patients with a sole diagnosis of asthma, resulting in higher costs for patients with ACO.³³⁻³⁵

This study indicates that around 65% of patients with difficult-to-control asthma have multiple comorbidities. This is relatively high in comparison with the general Dutch population with similar age, in which only around 45% of patients with a chronic disease have 2 or more comorbidities.³⁶ The association between a higher number of comorbid conditions and difficult-to-control asthma may have several explanations. First, conditions such as obesity, anxiety/depression, cardiovascular disease, and gastroesophageal

reflux may add to or interact with asthma symptoms, and may make it harder to understand what is the primary driver of symptoms, thus making it harder to achieve symptom control. Secondly, in some patients, the association between comorbidities and difficult-to-control asthma may be explained by increased perception of symptoms, including those of any comorbid conditions. Thirdly, comorbidities such as nasal polyposis that are often associated with chronic sinus infections may influence the underlying asthma mechanisms, and thereby asthma control and response to therapy. Finally, 1 in 4 patients with difficult-to-control asthma use chronic prednisone treatment that may also lead to comorbidities such as obesity, anxiety/depression, cardiovascular disease, and gastroesophageal reflux.^{37,38} Thus, many patients with difficult-to-control asthma are in a downward spiral: their comorbidities make asthma more difficult to control, whereas their asthma treatment leads to more comorbid conditions.³⁹

Our findings have clinical implications. Current guidelines on severe asthma emphasize the importance to address all potential aggravating factors, in particular adherence to medication, inhalation technique, and comorbidities in patients who are not controlled on high-dose ICS and bronchodilators.^{1,2,11} Our study confirms the importance of this recommendation, given the high prevalence of serious comorbidities that require screening, monitoring, and treatment in these patients. Future prospective studies are necessary to confirm that using a clinical risk profile in daily practice leads to earlier diagnosis and treatment of comorbidities with subsequent improvement in asthma control.

In conclusion, the majority of patients with difficult-to-control asthma have multiple and often serious comorbidities including cardiovascular disease, diabetes, anxiety/depression, obesity, and gastroesophageal reflux. Each particular comorbidity is associated with specific patient characteristics, of which older age, female gender, previous smoking, and chronic prednisone use are the most important. This emphasizes the necessity for routinely searching for comorbidities in patients with difficult-to-control asthma, so that these comorbidities are not overlooked and properly treated. Such approach is likely to reduce the burden for these patients as well as for the society.

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