

Current Control and Future Risk in Asthma Management

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Despite international and national guidelines, poor asthma control remains an issue. Asthma exacerbations are costly to both the individual, and the healthcare provider. Improvements in our understanding of the therapeutic benefit of asthma therapies suggest that, in general, while long-acting bronchodilator therapy improves asthma symptoms, the anti-inflammatory activity of inhaled corticosteroids reduces acute asthma exacerbations. Studies have explored factors which could be predictive of exacerbations. A history of previous exacerbations, poor asthma control, poor inhaler technique, a history of lower respiratory tract infections, poor adherence to medication, the presence of allergic rhinitis, gastro-oesophageal reflux disease, psychological dysfunction, smoking and obesity have all been implicated as having a predictive role in the future risk of asthma exacerbation. Here we review the current literature and discuss this in the context of primary care management of asthma.

Key Words: Asthma; control; disease exacerbation; primary health care

INTRODUCTION

The American Thoracic Society/European Respiratory Society (ATS/ERS) statement on asthma control defines asthma control as 'the extent to which manifestations of asthma are reduced or removed by treatment'.¹ This definition is further clarified into two components: current clinical asthma control and future risk. The level of clinical asthma control is defined according to symptoms, and the degree to which asthma impairs the individual's day-to-day activities and quality of life. Measures that are commonly used to quantify asthma symptoms in primary care are daytime and night-time symptoms, reduced activities, level of short acting β_2 agonist reliever usage and impaired lung function. The Global Initiative for Asthma (GINA) recommends using a composite measure comprising all of these 5 measures to enable stratification of disease control into: 'controlled', 'partly controlled' or 'uncontrolled'.²

While these measures give an indication of the current level of disease control, asthma control should also reflect the minimisation of future risk of exacerbation or of disease progression. An exacerbation is defined in the ATS/ERS statement on asthma control as an event that requires urgent intervention,¹ and is usually defined by the prescription of an acute course of oral

corticosteroids (OCS), hospitalisation or emergency room visit due to asthma. Exacerbations are the time of greatest risk to a patient, result in impaired quality of life and are a significant drain on healthcare budgets. Understanding factors predictive of exacerbation is therefore of great importance. Using a prospective survey study design, Guilbert et al.³ have recently reported that asthma that is not well controlled is associated with higher unscheduled healthcare resource use. In a retrospective analysis of the Gaining Optimal Asthma Control (GOAL) study database, Bateman et al.⁴ have also demonstrated that the degree of variability in asthma control is also associated with unscheduled healthcare resource use. Indeed, they showed that variability in asthma control is predictive of the use of unscheduled healthcare resource use, with higher variability in asthma control associated with a higher likelihood of unscheduled healthcare resource use.⁴ Bateman and colleagues⁵ have further

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reported that current asthma control is a predictor of future instability in asthma control and asthma exacerbations.

Despite national guidelines, poor asthma control remains highly prevalent. A recent pan-European cross-sectional survey found that in 2008, 57% of adult asthmatics had 'not well controlled' asthma on a validated symptom instrument, with no improvement since 2006.⁶ In a study conducted across 36 UK GP practices, Price et al.⁷ demonstrated that 36.5% of patients had an Asthma Control Questionnaire (ACQ) score of higher than 1.5, indicative of poor asthma control, and 14.2% had received one or more acute courses of oral corticosteroids in the previous 12 months. In a study using the Netherlands based PHARMO Record Linkage System, Breekveldt-Postma observed, in a study limited to patients with severe asthma, that 17% of patients showed lack of asthma control with costs related to asthma hospitalisations and excess therapies exceeding €10,000 per patient per year.⁸ In a recent US study Guilbert et al.³ reported that compared to adult asthmatics with well controlled asthma, over a 9 month period adults with baseline asthma that was not well controlled had significantly lower health related quality of life, were at three fold greater risk of an asthma related doctor visit and had a 10 fold greater risk of attending the emergency department because of asthma.

International (GINA, ATS and ERS) guidelines recommend that patients should be stepped up or down on a treatment algorithm to gain control and afford minimal symptoms and reliever usage.^{2,9-11} Several studies have explored the relationship between inhaled corticosteroids (ICS), long acting beta2 agonists (LABA) and asthma exacerbations. In the landmark FACET randomised clinical trial, Pauwels and colleagues reported that the higher dose of budesonide (800 µg per day) resulted in a significantly ($P=0.03$) greater reduction in severe exacerbations than those receiving the LABA formoterol in addition to low dose budesonide (200 µg per day; 49% vs. 26% $P=0.03$). In line with its bronchodilator activity, significantly more optimally-controlled days, less day-time rescue medication use and night-time symptoms were observed when formoterol was added to budesonide (low or high dose). Consistent with the results of the FACET study, in a retrospective cohort study using the General Practice Research Database (GPRD), Thomas et al.¹² compared the outcome of patients receiving LABA on a background of ICS compared to increasing the dose of ICS. After controlling for baseline differences and adjusting for confounders, patients receiving LABA were more likely to have improved symptomatic control and reduced bronchodilator usage but were found to be at higher risk of severe exacerbations and hospitalisations than those receiving an increase in ICS dose. This indicates that while bronchodilator therapy improved symptomatic control, reduction in exacerbation risk may require effective control of inflammation.

An ATS/ERS Task Force on outcome measures in asthma¹⁰ and GINA¹¹ have indicated that the objective of asthma man-

agement should be to 1) achieve current asthma control as defined by symptoms, reliever usage, activity and lung function; and 2) reduce future risk of exacerbations, loss of lung function or adverse medication effects. Reducing future risk of exacerbations is dependent upon the identification of predictive factors, and determining their relative influence on the future risk of exacerbations.

Here we discuss the literature on the prediction of exacerbations in conjunction with factors associated with difficult to treat asthma and frequent exacerbations, and discuss how they could be applied to the routine management of patients in primary care. Summaries of the factors associated with worst asthma control and future risk of poor asthma control are shown in Tables 1 and 2, respectively.

Factors associated with asthma exacerbations

Previous exacerbations

An acute asthma exacerbation (AAE) is usually defined as a worsening of asthma requiring a short course of OCS, visit to an emergency department or hospitalisation for asthma. Patients with a history of past asthma exacerbations have been reported to be at an increased risk of asthma exacerbations. Peters et al.¹³ reported that a history of an AAE is predictive of future AAE. Using GPRD to compare patients with or without hospitalisations in the outcome year, Price et al.¹⁴ reported that adults who had received 1 or more courses of oral corticosteroids in the baseline year, were 3 times more likely to have an asthma related hospitalisation during the following (outcome) year. The requirement for a short course of OCS has been shown to be predictive of future OCS need.^{8,15,16} Using The Epidemiology and Natural History of Asthma: Outcomes and Treatment Regimens (TENOR) database,¹⁷ Miller et al.¹⁸ reported that patients who have had a recent severe exacerbation requiring hospitalisation or an emergency room visit in the prior three months were at a 3-fold greater risk of future exacerbation compared to patients who have not had a recent severe exacerbation.

Asthma control

Asthma control is most often assessed through patient reported symptoms, reliever usage and, in some cases, including the GINA guidelines, lung function.^{2,13,19-21} Bateman et al.,⁵ in a retrospective analysis of five budesonide/formoterol maintenance and reliever therapy studies, reported that current asthma control in a given week, as assessed by the GINA-defined Asthma Control status,¹¹ can be used to predict the level of asthma control in the following week. They reported that the higher the level of poor asthma control in the index week, the greater the estimated probability of having an exacerbation in the following week. Bateman et al.⁵ also reported that poor asthma control at randomisation, assessed using the ACQ, is predictive of future risk of exacerbation. Poor asthma control (defined as 3-4 control problems on the Asthma Therapy Assessment Question-

Table 1. Summary of factors associated with worst asthma control

Factor	Study type	Patient group	Measure of Asthma Control	Results	P	Reference
Body Mass Index (BMI)	Interview and questionnaire study	Adults with moderate to severe asthma	ACQ	BMI < 25: 1.63 ± 0.09 BMI ≥ 25 < 30: 1.6 ± 0.08 BMI ≥ 30: 1.93 ± 0.1	F = 5.96 < 0.01	Lavoie et al. ⁵⁸
			AQLQ	BMI < 25: 5.18 ± 0.11 BMI ≥ 25 < 30: 5.17 ± 0.11 BMI ≥ 30: 4.84 ± 0.13	F = 6.30 < 0.01	Lavoie et al. ⁵⁸
Increase in weight			ATAQ	Adjusted odds ratio:		Haselkorn et al. ⁵⁷
			Acute Oral Steroids	1.22 (95%CI: 1.01-1.49)	0.04	
				1.31 (95%CI: 1.04-1.66)	0.02	
Gender			ATAQ; Exacerbations	Female worse	< 0.05; < 0.05	Haselkorn et al. ⁵⁷
Race	Historical Cohort Study (TENOR)	Adults with severe or difficult to treat	ATAQ; Exacerbations	Being black rather than white	< 0.05; < 0.05	Haselkorn et al. ⁵⁷
Employment			ATAQ; Exacerbations	Being disabled rather than full time employed	< 0.05; < 0.05	Haselkorn et al. ⁵⁷
Acute Course OCS in previous year			Acute Course OCS	Acute OCS in baseline year rather than no OCS	0.05	Haselkorn et al. ⁵⁷
Discontinuation of ICS (first 3 months)	Nested Case-Control study using Historical Cohort (Saskatchewan Health databases)	Age 5 to 44 years	Death	Adjusted rate ratio 4.6 (95%CI: 1.1-19.1)	< 0.05	Suisa et al. ⁶¹
Irregular use of ICS			Hospitalisation	Adjusted rate ratio 1.73 (95%CI: 1.41-2.11)	< 0.05	Suisa et al. ³⁰

TENOR, The Epidemiology and Natural History of Asthma: Outcomes and Treatment Regimens; ACQ, Asthma Control Questionnaire; AQLQ, Asthma Quality of Life Questionnaire; ATAQ, Asthma Therapy Assessment Questionnaire; OCS, oral corticosteroids; ICS, inhaled corticosteroids.

naire [ATAQ]) has been associated with increased risk of severe asthma related events,²² defined as oral steroid bursts, emergency room visits or a hospital admission. Poor asthma control has also been associated with increased acute-health care utilisation,¹³ although Peters et al.¹³ also reported that asthma control was not as strong a predictor of acute-health care utilisation as healthcare utilisation data (asthma related hospital admission and emergency room attendance). Consistently very poorly controlled asthma, defined by the impairment domain (including spirometry) of the National Heart Lung and Blood Institute (NHLBI) guidelines,^{23,24} compared to variably controlled asthma, has also been shown to be associated with a 6-fold increased risk of asthma exacerbation in children and a 3.2 fold increased risk of asthma exacerbation in adolescents or adults.²⁵ The concept of sub-acute lack of asthma control (SALAC) has been utilised in 2 studies. Using administrative claims databases (Patient Centric Database [PharMetrics/IMS Health Inc., Watertown, MA, USA] and HealthCore Integrated Research Database [HealthCore Inc., Wilmington, DE, USA]), and defining SALAC as requiring more than 5 prescriptions of reliever therapy in a year or having attended their primary care physician on more than 4 occasions in a year, O'Connor et al.¹⁶ and Stephenson et al.¹⁵ reported SALAC as being predictive of future exacerbation. However, due to limitations in the data available, no further analyses of additional contributory predictive factors was possible.

Inhaler technique

The correct use of inhaler devices, is essential for optimal drug delivery and clinical benefit.²⁶ However, poor inhaler technique remains common²⁶ and has been associated with increased unscheduled health-care resource use and poor asthma control.²⁷ Despite this, inhaler technique status has not been included in most analyses aimed at identifying risk factors predictive of future exacerbations.

Lower respiratory tract infections and recurrent respiratory infections

There is a growing body of evidence concerning the role of bacterial infections in asthma.²⁸ Lower respiratory tract infections requiring antibiotics are not usually included in the definition of an exacerbation however. Although a visit to a primary care provider resulting in a prescription of antibiotics would be captured by measuring attendances at primary care providers, the attendance would not indicate the severity of an exacerbation as would be indicated by an antibiotic prescription. Using the GPRD, Price et al.²⁹ reported in a matched analysis that 19% of patients with mild to moderate asthma had received antibiotics for a lower respiratory infection in the baseline year, compared to 16% receiving ≥ 1 acute courses of oral corticosteroids. Research is required to determine the value of including lower respiratory tract infections in the definition of an exacerbation.

Table 2. Summary of factors associated with future risk of poor asthma control

Factor	Study type	Patient group	Predictive of:	Odds ratio	P	Reference
Exacerbations*	Historical Cohort Study (Health Care Plan: Pharmetrics)	Aged ≥ 12 yr	Exacerbations* only	2.503 (2.176-2.879)	<0.0001	O'Connor et al. ¹⁶
			Exacerbations AND ≥6 SABA [†]	3.394 (3.009-3.827)	<0.0001	
Hospitalisation	Questionnaire & Historical Cohort Study (Health Care Plan: K-P)	Adults	High SABA usage	1.4 (1.2-1.7)	0.0004	Schatz et al. ⁵²
Oral corticosteroid use	Historical Cohort Study (GPRD) Historical Cohort Study (GPRD) Questionnaire & Historical Cohort Study (Health Care Plan: K-P)	Adults Children 6-15 yr Adults	Hospitalisation	3.01 (1.90-4.78)	<0.0001	Price et al. ¹⁴
			Hospitalisation	2.24 (1.08-4.67)	0.0314	Thomas et al. ³⁵
			High SABA usage	1.9 (1.4-2.5) for >2 acute courses OCS in baseline year	<0.0001	Schatz et al. ⁵²
Variability in asthma control	Retrospective analysis of Randomised Controlled Trial (GOAL)	Aged ≥ 12 yr	Unscheduled health- care resource use	1.06 (1.05-1.07)	<0.001	Bateman et al. ⁴
Poor asthma control (Asthma Control Questionnaire ≥ 1.5)	Retrospective analysis of 5 budesonide/formoterol maintenance and reliever therapy studies	Aged 4 to 89 yr	Exacerbations* (events/patient/year)	ACQ ≥ 1.5: 0.36 (95% CI:0.09-0.20) ACQ <0.50: 0.13 (95% CI:0.09-0.20)	<0.001	Bateman et al. ⁵
Female gender	Historical Cohort Study (GPRD) Historical Cohort Study (Health Care Plan: Pharmetrics)	Adults Aged ≥ 12 yr	Hospitalisation	1.56 (1.09-2.22)	0.0155	Price et al. ¹⁴
			Exacerbations*	1.329 (1.224-1.443)	<0.0001	O'Connor et al. ¹⁶
Male gender	Questionnaire & Historical Cohort Study (Health Care Plan: K-P)	Adults	High SABA usage	1.5 (1.3-1.8)	<0.0001	Schatz et al. ⁵²
Age	Cross-sectional survey	Adults	ACQ ≥ 1.5	1.01 (1.01-1.02)	<0.001	Clatworthy et al. ³¹
Age 12 to 17 yr vs. 45-54 yr or vs. ≥55 yr	Historical Cohort Study (Health Care Plan: Pharmetrics)	Aged ≥ 12 yr	Exacerbations*	0.836 (0.742-0.942)	0.0032	O'Connor et al. ¹⁶
				0.841 (0.727-0.973)	0.0199	
Allergic rhinitis	Historical Cohort Study (GPRD)	Adults	Hospitalisation	1.52 (1.03-2.24)	0.0365	Price et al. ¹⁴
		Children 6-15 yr	Hospitalisation	2.34 (1.41-3.91)	<0.0011	Thomas et al. ³⁵
Mild rhinitis	Cross-sectional survey	Adults	ACQ ≥ 1.5	2.09 (1.72-2.54)	<0.001	Clatworthy et al. ³¹
Severe rhinitis			4.62 (3.71-5.77)	<0.001		
SABA prescriptions	Historical Cohort Study (GPRD)	Adults	Hospitalisation	1.15 (1.10-1.21)	<0.0001	Price et al. ¹⁴
		Children 6-15 yr	Hospitalisation	1.25 (1.13-1.39)	<0.0001	Thomas et al. ³⁵
≥6 SABA prescriptions/yr	Historical Cohort Study (Health Care Plan: Pharmetrics)	Aged ≥ 12 yr	Exacerbations*	1.277 (1.166-1.399)	<0.0001	O'Connor et al. ¹⁶
+ >4 physician visits in the yr	Historical Cohort Study (HealthCore Integrated : Research Database)	Aged ≥6-64 yr	Exacerbations*	1.601 (1.514-1.692)	<0.001	Stephenson et al. ¹⁵
≥6 SABA prescriptions/yr	Historical Cohort Study (HealthCore Integrated : Research Database)	Aged ≥6-64 yr	Exacerbations*	1.854 (1.719-2.000)	<0.001	Stephenson et al. ¹⁵
>4 physician visits in the yr		Aged ≥6-64 yr	Exacerbations*	1.340 (1.249-1.438)	<0.001	Stephenson et al. ¹⁵
Low dose ICS	Historical Cohort Study (GPRD)	Children 6-15 yr	Hospitalisation	1.81 (1.05-3.14)	0.0334	Thomas et al. ³⁵
Medium dose ICS		Adults		1.76 (1.13-2.74)	0.0119	Price et al. ¹⁴
High dose ICS		Adults		2.26 (1.04-4.94)	0.0408	Price et al. ¹⁴
≥800 µg/day		Children 6-15 yr		5.60 (2.11-14.88)	0.0005	Thomas et al. ³⁵
Low adherence	Cross-sectional survey	Adults	ACQ ≥ 1.5	1.35 (1.18-1.55)	<0.001	Clatworthy et al. ³¹
Weight gain (≥5 lb)	Historical Cohort Study (TENOR)	Severe or difficult to treat adults	Acute course OCS	1.31 (1.04-1.66)	<0.02	Haselkorn et al. ⁵⁷
Active smoking	Cross-sectional survey	Adults	ACQ ≥ 1.5	4.33 (3.58-5.23)	<0.001	Clatworthy et al. ³¹
	Questionnaire & Historical Cohort Study (Health Care Plan: K-P)	Adults	High SABA usage	2.2 (1.7-3.0)	<0.0001	Schatz et al. ⁵²
Past smoking history	Cross-sectional survey	Adults	ACQ ≥ 1.5	1.59 (1.36-1.87)	<0.001	Clatworthy et al. ³¹

*Acute course of OCS OR emergency room attendance for asthma OR hospitalisation for asthma.

[†] ≥6 SABA prescriptions/year AND/OR >4 physician visits in the year.

GPRD, General Practice Research Database; SABA, Short acting beta2 agonist; ICS, Inhaled corticosteroid; KP, Kaiser-Permanente Medical Care Program; GOAL, Gaining Optimal Asthma Control; TENOR, The Epidemiology and Natural History of Asthma: Outcomes and Treatment Regimens; ACQ, Asthma Control Questionnaire.

Adherence to therapy

Good adherence to asthma therapy is essential for maximal therapeutic benefit and avoidance of exacerbations. Regular use of low-dose inhaled corticosteroids has been shown to reduce the risk of death and hospitalisations. Using the Saskatchewan Health databases (Government of Saskatchewan, Saskatchewan, Canada) and a nested case-control study design, Suissa et al.³⁰ reported the mean number of canisters of low dose inhaled corticosteroids used in the year prior to date of death (or index date) was 1.18 in patients who had died due to asthma compared to 1.57 canisters in the matched control group, and that the rate of death decreased by 21% with every one additional canister of ICS used in the year prior to death (rate ratio: 0.79; 95% CI: 0.65 to 0.97). Exploring death rates following discontinuation of ICS, Suissa et al.³⁰ reported a four-fold increase in the rate of death in the three months immediately following discontinuation of ICS compared to those that had continued their ICS. In terms of hospitalisations, in a further analysis of the same database, Suissa et al.³⁰ reported that in the 12 months following initiation of ICS, irregular use of ICS was associated with a 73% increase in the rate of hospitalisations, compared to those who took their ICS regularly. Regular use of ICS over at least a 4 year period further reduced the rate of hospital admissions by 31% compared to those who used their ICS irregularly or not at all (rate ratio: 0.69; 95% CI: 0.57-0.83). Bateman et al.⁴ reported that once control of asthma is achieved, control is more likely to be maintained where adherence to therapy is good. The inclusion of measures of adherence to therapy in studies evaluating factors predictive of asthma exacerbations has been variable. Haselkorn et al.²⁵ utilised patient reported medication compliance, although this was not validated with administrative claims data. In a questionnaire study, Clatworthy et al.³¹ reported that poor asthma control was associated with self-reported low medication adherence.

Allergic rhinitis and allergies

The link between rhinitis and asthma is well recognised³² with 60% of asthmatics having concomitant allergic rhinitis, and 20-30% of people with rhinitis having concomitant asthma.³³ Co-existing rhinitis and asthma can impact significantly on patient quality of life and health care costs.³⁴ Using the GPRD database, Price et al.¹⁴ reported that adults with concomitant allergic rhinitis and asthma experienced significantly more GP visits, more asthma-related hospitalisations and higher asthma related drug costs than patients with asthma alone. Furthermore, they reported that patients with concomitant allergic rhinitis were 1.52 fold more likely to have an asthma-related hospitalisation than those with asthma alone.¹⁴ In children with asthma aged 6-15 years, concomitant allergic rhinitis increased the likelihood of a hospitalisation for asthma 2.34 fold to that of a child with asthma alone.³⁵ In agreement with the adult study, compared to children with asthma alone, those with asthma and

concomitant allergic rhinitis had a higher number of GP visits and higher asthma related drug costs. Treatment of allergic rhinitis in patients with concomitant asthma has also been shown to improve both asthma and rhinitis control. In patients with concomitant asthma, after adjusting for baseline differences, treatment of allergic rhinitis using the nasal corticosteroid mometasone, were found to have significant improvements in both rhinitis control and asthma control compared to matched parents receiving oral antihistamines, although the authors were unable to identify the variable responsible for driving the improvement in asthma control.³⁶

Significant untreated rhinitis has been significantly associated with poor asthma control.³⁴ Conversely, Breekveldt-Postma et al.⁸ reported that treatment of allergic rhinitis with nasal preparations (corticosteroids or anti-allergic compounds) was not significantly associated with uncontrolled asthma in patients with severe asthma, suggesting that active treatment of rhinitis facilitates improved asthma control. Comparing patients with continued very poorly controlled asthma to those who had an improvement during the study, Haselkorn et al.²⁵ reported no difference in the proportion of patients with a history of allergic rhinitis at baseline. However it was not reported whether patients were receiving nasal preparations for allergic rhinitis or the level of symptoms experienced. In a separate study, Haselkorn et al.³⁷ identified predictors of severe exacerbations in children. They reported that patients with 3 to 4 allergic triggers (from pollen, dust, pets and mold) were at 2 fold higher risk of future asthma exacerbation compared to those who with no allergic triggers. In a questionnaire study, Clatworthy et al.³¹ reported that those with self reported rhinitis (severe or mild) were more likely to exhibit poor asthma control dependant on the severity of the rhinitis.

Gastro-oesophageal reflux disease

A recent systematic review reported an estimated prevalence of GORD symptom ranging from 30-90% in asthmatics compared to 10-20% in the general population. People with asthma had 5 times the risk of having GORD symptoms, and those with GORD had double the risk of asthma.³⁸ Despite this high frequency, a history of symptoms or treatment of GORD has not been included in most analyses aimed at identifying risk factors predictive of future asthma exacerbations. Using the TENOR study database Chen et al.³⁹ reported that the presence of 1 or more major co-morbidities was a significant independent predictor of reduced general health status (using EQ-5D), but not of asthma specific quality of life (assessed using Mini-AQLQ), although they did not define the co-morbidities included. A further analysis of the TENOR study database limited the major co-morbidities included to chronic obstructive pulmonary disease, bronchitis and emphysema.²⁵

Psychological dysfunction

There is considerable literature on the relationship between asthma and psychological dysfunction.⁴⁰ Although anxiety is a normal response to asthma symptoms, excessive anxiety may lead to hyperventilation and subsequently cause airways cooling and bronchoconstriction.⁴¹ Cross-sectional surveys have shown that, independently of objective asthma severity and other confounding factors, anxiety and depression influences symptomatic control and asthma related health status.^{42,43} Fear of the physical symptoms of uncontrolled asthma has been suggested to be linked to poor asthma control. In a recent study of anxiety sensitivity in asthma control, McLeish et al.⁴⁴ reported that the physical concern domain of the Anxiety Sensitivity Index-3 was significantly negatively associated with asthma control as assessed by the Asthma Control Test. Worse asthma control, in terms of higher asthma hospitalisation rates,⁴⁵⁻⁴⁷ higher asthma related mortality⁴⁸ as well as less successful asthma emergency treatment⁴⁷ have been associated with asthmatic patients with psychological dysfunction compared to those with asthma alone. In patients with severe asthma, ten Brinke and colleagues reported higher asthma related health care utilisation in patients with psychological dysfunction.⁴⁹ In a separate study, ten Brinke et al.⁵⁰ reported no difference in the psychological characteristics of patients with mild or severe asthma, but that compared to patients with mild asthma those with severe asthma were more likely to lack trust (or had a lower level of trust) in their asthma physician and asthma medication.

Smoking

The probability of having poorly controlled asthma has been shown to be 2.7 fold greater in asthmatics who are active smokers compared to non-smokers and 1.27 fold greater in ex-smokers compared to non-smokers.⁵¹ In agreement, Schatz et al.⁵² reported that active smokers were more likely to have poor asthma control, based on SABA canister dispensing, compared to non or ex-smokers. Haselkorn et al.²⁵ were unable to report the impact of active smoking on future risk of asthma exacerbation as no active smokers were identified in their 'improved from very poorly controlled asthma' cohort at baseline. Sullivan et al.²² and Peters et al.¹³ did not report smoking status. For the study reported by O'Connor et al.,¹⁶ the PharMetrics database did not hold smoking information. In a questionnaire study, Clatworthy et al.,³¹ reported that poor asthma control was associated with self-reported smoking.

Obesity

High body mass index (BMI) has been shown to be associated with both increased incidence of asthma and increased asthma severity.⁵³⁻⁵⁵ In terms of asthma control, Barros et al.⁵⁶ and Haselkorn et al.⁵⁷ reported that asthma control is significantly worse in patients with a high body mass index. Furthermore, Haselkorn et al.⁵⁷ reported that patients who gained at least 5 lb (2.27

kg) or more during the 12 month study period had significantly poorer asthma control, worse quality of life and more acute courses of oral corticosteroids than patients who had either maintained their weight or lost at least 5 lbs (2.27 kg), suggesting that weight gain maybe a causal factor for poor asthma control. However in terms of future risk of exacerbations, using the TENOR study database, both Haselkorn et al.⁵⁷ and Sullivan et al.²² reported no association between obesity (defined as a BMI ≥ 30) and future risk of asthma exacerbation, although neither studies reported whether further stratification into obese, very obese or morbidly obese categories was undertaken possibly due to small patient numbers. Lavoie et al.⁵⁸ reported that higher BMI was associated with worse asthma control and quality of life, but in contrast to the above studies, after controlling for age and gender, they found no association between BMI and asthma severity. However, this discrepancy may be due to a selection bias, as all patients participating in the Lavoie et al. were recruited from a hospital based asthma clinic and would therefore be expected to have moderate to severe asthma. Studies of larger patient numbers are required to explore the interaction of obesity and future risk of asthma exacerbation.

Limitations of studies to date

Many of the studies we have reported here have limitations. In terms of questionnaire studies, these studies are limited by the common issues surrounding questionnaire use: skewed demographics and inconsistent response rates. Peters et al.¹³ reported that of the 62% of 13,964 patients surveyed using the ATAQ, only 5,172 were eligible for the study. In contrast, Lai et al.⁵⁹ used an interviewer technique to obtain patient reported questionnaire data in which prospective participants were approached either by door-to-door recruitment, street interception or peer referral. However, this high cost, high intensity approach is not practical in routine primary care. Sullivan et al.²² utilised TENOR database in which detailed phenotypic data, including exacerbations, treatment and laboratory measures of patients with severe or difficult to treat asthma were recorded on a 6 monthly basis.¹⁷ This prospective database is arguably the nearest to capturing of data as part of routine care, but is limited by 1) its short duration: 2001 to 2004; 2) possible selection bias in that only patients with severe or difficult to treat asthma were recruited and those without access to healthcare were ineligible, and 3) potential recall bias as healthcare utilisation data was patient reported and not verified with administrative claims data.

Many studies have utilised managed care claims and health plan enrolment databases.^{16,52,60} As O'Connor et al.¹⁶ describes, these are limited by potential selection bias inherent to claims databases. As continuous members of a healthcare plan, these patients are more likely to have been in continuous employment, compared to the average population. Also symptom, spirometry, controller therapy adherence, socioeconomic status and

race/ethnicity data are unavailable in these databases making analyses beyond asthma severity, and disease control using exacerbations and SABA usage very difficult, if not impossible.

Further improvements in the understanding of asthma control and the prediction of future risk will require the use of highly descriptive routine primary care databases complemented by patient reported questionnaire data. These databases should ideally have a large enough population to allow for identification of possible sub-groups of patients at risk of exacerbation, but also have extensive data to facilitate high quality, meaningful research. We await the results of these studies.

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