

REVIEW

Defining and managing risk in asthma

J. D. Blakey¹, S. Zaidi² and D. E. Shaw³¹Clinical Sciences, Liverpool School of Tropical Medicine, Liverpool, UK, ²Respiratory Medicine, Aintree University Hospital NHS Trust, Liverpool, UK and³Department of Respiratory Medicine, University of Nottingham, Nottingham, UKClinical
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Summary

Asthma attacks are a major global source of morbidity and cost. The incidence and impact of asthma attacks have not improved despite widespread adoption of effective universal treatment guidelines. Consequently, there is increasing interest in managing asthma based on specific assessments of both current symptoms and future risk. In this review, we consider 'risk' in asthma, and how it might be assessed from the patient's history and objective measurements. We also discuss the potential for encouraging shared decision-making and improving medical consensus through explicit communication of risk and highlight the potential opportunities and challenges in risk assessment to improve asthma management through individualised treatment strategies.

Correspondence:

Dr Dominick E. Shaw, Department of Respiratory Medicine, Clinical Sciences Building, City Hospital Campus, Nottingham NG5 1PB, UK.

E-mail: Dominic.shaw@nottingham.ac.uk

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Introduction

Asthma is defined as a 'chronic inflammatory disorder of the airways...in susceptible individuals, and inflammatory symptoms are usually associated with widespread but variable airflow obstruction and an increase in airway response to a variety of stimuli. Obstruction is often reversible, either spontaneously or with treatment' [1]. Whilst this definition describes the usual combination of symptoms and pathophysiological findings, it tells us little about the clinical course of asthma and is not directly applicable in common situations where indices of airway inflammation and hyper-responsiveness are not routinely available. Most asthma is managed in primary care where the disease is defined practically as symptoms of cough, wheeze and breathlessness, and treatment response is assessed by improvement in these symptoms. This approach is found wanting if there is a poor correlation between pathophysiology and symptoms or when the diagnosis is either incorrect or incomplete, moreover it does not consider future risk.

Asthma attacks

The main risk in asthma is of acute exacerbations (asthma attacks), with deterioration in both symptom

control and objective measures of airflow obstruction [2]. As asthma is a common chronic disease [3], this represents a major worldwide public health issue. Asthma attacks are responsible for tens of thousands of admissions each in the United Kingdom [4] and many more consultations in primary care [5]. These attacks are associated with significant morbidity, accelerated loss of lung function [6–8], adverse effects of medications [9, 10] and the psychological effects of an abrupt and distressing decline in function in an usually otherwise healthy adult [11]. Around 1500 deaths per annum in the United Kingdom are coded as being due to asthma [12]. The effects are felt beyond those with asthma: the direct hospital and medication costs and resultant loss of productivity (indirect costs) related to asthma attacks run into billions of pounds [13]. Despite advances in asthma care and the widespread adoption of standard, guideline-based treatment, adverse outcomes are not in decline [14]. This is unacceptable given that only a small proportion of asthma is truly refractory to treatment [15].

Both guidelines [16, 17] and commonly used asthma assessments [18, 19] predominantly focus on symptom control with a secondary consideration of future risk. One may therefore deduce that the current guidelines are not being adhered to, or the treatment strategy they recommend has limited efficacy in improving the

incidence of asthma attacks. In either case, the guidelines could be more effective; considering risk in asthma management might achieve this improvement [20–22].

Defining risk

We all make daily decisions that impact on future outcomes, despite the future being uncertain. These decisions are based on past experiences (heuristics), current emotion and cultural context rather than a simple objective appraisal of probabilities and gains [23]. Where there are little data available to guide a decision ('technical uncertainty') [24], the influence of biases and heuristics is inevitably greater. These biases tend to lead to an underestimate of the risks associated with voluntary or pleasurable activities, but an intolerance of risks that are perceived to be beyond one's control or where the risk is not well defined [25]. We also undervalue more mundane things which carry a greater cumulative risk [26, 27]: For example, one skydive carries about the same risk of death as someone (cumulatively) riding 100 miles on a bike [28]. These issues around risk perception illustrate that challenges lie not only in empirically assessing risk in asthma, but also in employing the information objectively and communicating it effectively.

We think of risk as the chance of an adverse event given a hazard; a loss is an undesirable event (such as cutting a finger), and a hazard is a potentially damaging exposure or activity (such as chopping vegetables). Negative outcomes in asthma such as an admission, lung function impairment or psychological dysfunction could evidently be considered losses; however, the perception of their impact may differ between physician and patient. Although physicians are most concerned about symptoms and attacks, patients may fear medication-related side effects, time off work and negative social labelling. This difference in perception may partly explain the excess number of asthma exacerbations; patients may see an occasional exacerbation as preferable to lifelong daily asthma treatment. Clarifying what risk we are concerned about and the relative importance of such outcomes to the patient is central to asthma management.

Symptoms, control and future risk

Gaining control of asthma symptoms is the focus of international and national guidelines, including the BTS/SIGN and GINA documents [16]. Although these guidelines do discuss future risk and there is greater clarity around both clinical and study exacerbation outcomes [29], it is loss of daily symptom control that is still the main trigger for escalation of treatment.

Commonly used scales such as the RCP 'Three Questions' [30], Asthma Control Questionnaire [19] and Asthma Control Test [18] also focus on symptom control as a measure of the adequacy of management. Although at a population level, those with better control of their asthma symptoms are less likely to have an asthma attack, and are less likely to have airway inflammation or damage [31–33], this is not necessarily true at an individual level. For example, a study of pooled trial data from several thousand individuals found current control was not associated with the risk of a future asthma attack after controlling for potential confounders [34].

Asthma is a heterogeneous syndrome with a variety of overlapping subtypes [35]. Some individuals display greater airways hyper-reactivity with frequent symptoms, whereas others have a greater risk of asthma attack and more airways inflammation [36]. In addition, perception of pathology varies between individuals [37], and comorbidities that influence symptoms are not uniformly distributed [38]. Population measures of control therefore have wide confidence intervals when related to risk [39] and are indicative of a relationship similar to that shown in Fig. 1. Consequently, measuring control alone does not permit predictions of future adverse outcomes at an individual level.

Most individuals with asthma will achieve adequate control of symptoms and objective measures of airway dysfunction if they are able to take inhaled steroid and long-acting beta-agonist therapy appropriately. Those that do not respond to this regimen are generally considered to have severe asthma [40]. Such individuals have, overall, a greater risk of asthma attack than those with more mild disease, but are no more homogeneous as a group [15]. Commonly employed measures of

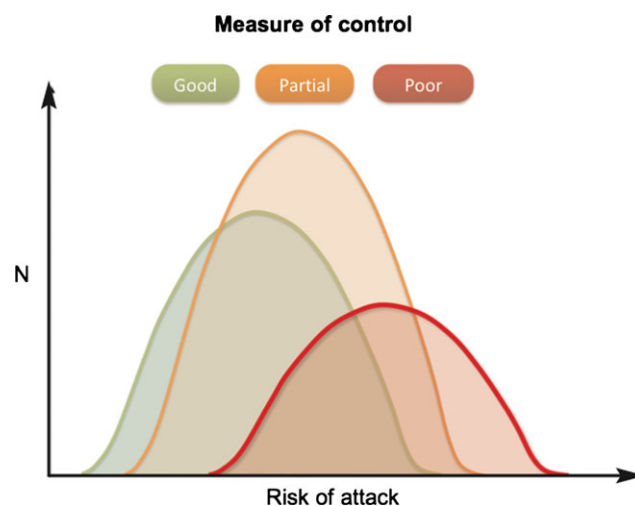


Fig. 1. Schematic to illustrate the risk of asthma attack for populations of asthma patients with good, partial and poor asthma control.

asthma severity are poor predictors of near-fatal asthma, and of admissions within those with difficult-to-treat asthma [41, 42].

The relationship between symptoms and risk of attack is further complicated by the prevalence of misdiagnosis. In primary care, around one-third of patients with a label of asthma have no evidence of airway hyper-responsiveness or airflow obstruction [43, 44]. This discrepancy arises in part because patients are often treated as part of the diagnostic process: in the United Kingdom, half of those with asthma receive regular treatment before the objective evidence of disease is confirmed [45]. The situation is similar in secondary care where many patients labelled as having difficult asthma have alternative or major additional diagnoses [46].

Assessing risk

Although clinicians may already consider future risk to some degree, this assessment is usually not systematic and is limited to a small number of major modifiable risk factors (such as those in Table 1). Such risk assessments do not consider overall risk and the proportion that is modifiable. Figure 2 shows a schematic of the risk trajectories of two individuals with asthma illustrating differing influences of various modifiable and fixed risk factors can lead to a similar cumulative risk, but potentially very different responses to treatment.

A compartmentalised approach will also overlook the interaction of risk factors that are not simply additive, for example, the beneficial effects of adding LABA to ICS are modulated by obesity [47]. Less emphasis is also often placed on risk factors that lie outside our own expertise (e.g. psychological issues, effect of neonatal

insults). Finally, as the emphasis of guidelines (or at least their summaries) is towards escalating drug treatment, non-pharmacological interventions are under-employed: for example, approximately 3 h of a healthcare professional's time spent on educating individuals about asthma will prevent an admission [48], but few centres have such programmes. However, it is routine to spend heavily on adding a long-acting beta-agonist to inhaled corticosteroids, a step that does not appear to greatly alter the risk of admission, but does improve symptoms [49].

A more systematic and mathematical method of quantifying risk may help clinicians and patients to make better informed (and potentially healthier) decisions. Undertaking such as assessment of an individual's future risk is a challenging endeavour. However, existing data could provide a robust starting point. For example, information from large studies such as FACET [50] and GOAL [51] that measured exacerbation rates over time could be used to derive estimates of baseline risk stratified by treatment. Pooled data from clinical trials have already shown that the relative risk for an asthma exacerbation in patients who stopped their ICS compared with those who continued use was 2.35 (95% CI, 1.88–2.92; $P < 0.001$). The pooled absolute risk difference for an asthma exacerbation was 0.23 [52]. From a practical perspective, this means only one in five patients with stable asthma who stop low-dose ICSs will have an exacerbation in the next 6 months that is attributable to stopping the ICS, information that patients are likely to find very helpful.

Further instructive data lie within large-scale primary care records, leveraged through systems such as The Clinical Practice Research Datalink (CPRD). Robust information has already been produced on key factors

Table 1. Common risk factors that may be elicited in the asthma clinic, and examples of studies assessing the risk they confer

	Risk factor	Example studies	Potential intervention (s)
Symptoms	Poor daily control	Dennis <i>et al.</i> [93]	Numerous; e.g. increase preventer therapy,
	Night-time symptoms	Lehtimäki <i>et al.</i> [94]	improve concordance
History	Age	Skobeloff <i>et al.</i> [95]	Non-modifiable
	Uncontrolled allergic/atopic disease	Bousquet <i>et al.</i> [96]	Nasal steroids, immunotherapy, antifungal agents
	Tobacco exposure	Chilmonczyk <i>et al.</i> [97]	Smoking cessation services for patient or close contact
	Pollutants	Lee <i>et al.</i> [98]	Relocation for individual, legislation to reduce pollution
	Poor medication concordance	Williams <i>et al.</i> [99]	Discussion of barriers, motivational interviewing
	Excessive use of beta-agonists	Naureckas <i>et al.</i> [100]	Increase preventative therapy, asthma management plan
	Socioeconomic status	Bacon <i>et al.</i> [101]	Non-modifiable
	Psychological comorbidity	Sandberg <i>et al.</i> [102]	Screening questionnaire, referral to appropriate speciality
	Poor understanding of asthma self-management	Cowie <i>et al.</i> [103]	Consultation, asthma action plan, directions to sources of information
Investigations	Airflow obstruction	Fuhlbrigge <i>et al.</i> [104]	Optimise treatment, may be non-modifiable
	BMI	Stenius-Aarniala <i>et al.</i> [105]	Identify issue, refer to weight loss programmes
	Perception of dyspnoea	Magadle <i>et al.</i> [106]	Biofeedback approach using serial peak flows
	Airway inflammation	Green <i>et al.</i> [71]	Induced sputum measurement

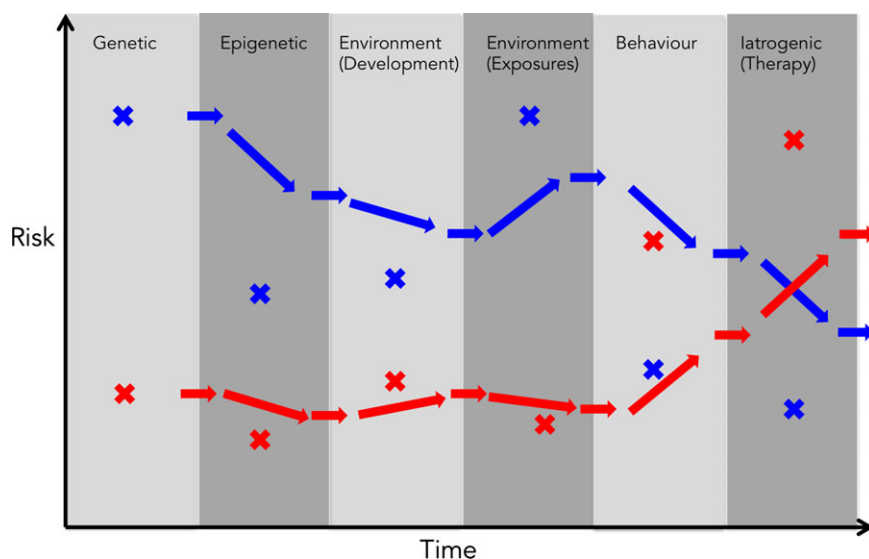


Fig. 2. Schematic illustrating risk trajectories for two individuals with asthma. The crosses indicate the risk for each influence, and the arrows indicate the individual's total risk. One individual is shown in red, the other in blue.

such as the influence of add-on therapies and choice of inhaler device on subsequent asthma attack rates [53, 54]. Given these resources, the development of a formal risk assessment tool is challenging but feasible.

What can we learn from other diseases?

Asthma is unusual amongst chronic diseases as it is managed predominantly according to reported symptoms. This is the antithesis of the approach taken in cardiovascular medicine where simple calculations are routinely employed to assess the risk of future stroke or myocardial infarction [55]. These assessments are supported by objective evidence of future risk from invasive and expensive investigations such as specific biomarkers, angiography and MRI. Individuals at risk are then prescribed preventative medication for risk factors such as hypertension and hypercholesterolaemia, which have no beneficial effect on their daily symptoms but may cause side effects. Symptoms trigger risk assessment, but aggressive interventions such as bypass surgery are restricted to those with appropriate pathology rather than the worst symptoms. This acceptance of the disengagement between symptoms and pathophysiology also identifies patients who are not at risk despite symptoms and helps reduce inappropriate treatment and anxiety. The results of this strategy are evident; admissions for myocardial infarction and related mortality have approximately halved in the past 25 years [56, 57].

Assessing risk and instigating regular objective monitoring occurs in other prevalent chronic diseases such as diabetes: It would seem extraordinary to manage type 1 diabetes without home glucose measurements

and screening for complications. However, these developments [58] arrived decades after induced sputum eosinophil counts and peak flow monitoring [59, 60], neither of which are regularly used by the majority of asthma sufferers.

Incorporating risk into treatment selection

It is well recognised that treatments act differently on daily symptoms and future risk (Fig. 3). A striking example of this is the monoclonal antibody mepolizumab. It had no effect on symptoms and airways hyper-reactivity measures in initial studies that included individuals with bronchial hyperactivity [61]. Subsequent trials in individuals at high risk of asthma attack showed a striking benefit on this outcome [62]. Similarly, discrepant effects are seen for other interventions, both old [63] and new [64].

This unequal effect should have a significant impact on our practice. For example, a patient on low-dose inhaled corticosteroid therapy may be stepped up to a higher dose or have a long-acting beta-agonist added. The former option would have a greater effect on reducing the risk of asthma attack, and the latter would have a greater effect on symptoms [50]. The choice should therefore be driven by the reason for wishing to step up treatment (attacks or variable peak flows), success should be measured by that outcome and the expectations conveyed to the patient should be commensurate.

An explicit recognition of the differential effects of treatments also has the potential to reduce drug-related harm. Avoiding treatments that are unlikely to be of benefit removes the potential for unnecessary adverse

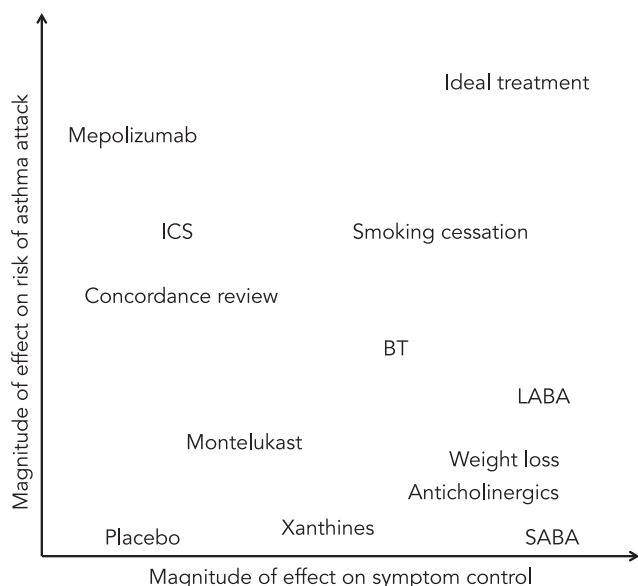


Fig. 3. Schematic illustrating the likely effect of interventions on symptom control and future risk. LABA, long-acting beta-agonist; SABA, short-acting beta-agonist; BT, bronchial thermoplasty; ICS, inhaled corticosteroids. The placement of BT in the figure includes the apparent initial increase in the risk of asthma attack in the period following the procedure.

effects. The selection of medication for asthma also highlights the potential to take non-modifiable risk factors into consideration. Common genetic polymorphisms have significant effects on the therapeutic potential or probability of side effects from frequently prescribed medications, featuring on FDA-approved drug labels for clopidogrel, carbamazepine, atorvastatin and rifampicin amongst many others [65]. Although specific variants altering the response to common inhaled drugs have not yet been robustly identified, ethnic background should influence asthma prescription decisions [66]. The use of genetic information to stratify patient prescribing is likely to become widespread as technology permits a DNA test to be completed cheaply and quickly from a small amount of blood or buccal swab.

Risk-based strategies in asthma

Although current guidelines advocate a symptom-based treatment algorithm, there is support for alternative strategies that primarily aim to reduce the risk of asthma attack.

Measuring airway inflammation

Asthma exacerbations are characterised by limited response to bronchodilators and the need for anti-inflammatory therapy. Measurement of airway inflammation by sputum eosinophil count is closely associated

with both response to steroids, and the probability of exacerbation if they are stopped [67, 68]. Moreover, significant increases in the sputum eosinophil count occur before the onset of clinical features of exacerbations [69]. This work led to studies assessing the use of treatment algorithms altering steroid dose on the basis of differential sputum cell counts. Treating airway eosinophilia in this way has consistently been shown to reduce asthma exacerbations [70]. What is often not appreciated is that in the original trial [71], both regular management and sputum-based treatment strategies achieved equivalent control of symptoms, quality of life and disordered airway function, again reflecting the concept that symptoms and risk of attack are not synonymous.

Using an induced sputum-based approach to risk management has not been widely adopted. This may reflect the difficulty in establishing appropriate laboratory services for its delivery. Other surrogate markers of airway inflammation have been employed, particularly point of care testing of exhaled nitric oxide (FENO), with differing degrees of success [72]. In a study of pregnant women, a FENO-based management approach reduced asthma exacerbations (again with no effect on quality of life measures). Inference from this study is limited by the non-standard treatment provided for the control group [73], and FENO-based management has been disappointing in other large clinical studies [74]. Blood eosinophil count may prove to be a practically more useful proxy of airway inflammation as it is readily measured in most settings and is associated with response to corticosteroids in both asthma and COPD [75].

The use of induced sputum as a tool in categorising asthma is appealing as single (or at least infrequent) measurements can be made at specialist centres and patients tend to remain in one inflammatory-type group [76]. Understanding the amount and type of inflammation has implications for future risk and related management strategies, and may inform the use of biologic agents in refractory asthma [77, 78].

Reducing exposure to drivers of airway inflammation. Asthma is considered an atopic disease and is often driven by inhaled aeroallergens [36]. General allergen reduction interventions would therefore seem logical, but do not appear to be successful [79], although definitive studies on laminar flow devices are awaited [80]. This lack of effect appears to relate to the practical problem of reducing allergen exposure outside the home. Ameliorating allergic inflammation through the administration of anti-IgE monoclonal antibody or subcutaneous immunotherapy circumvents this issue. Both these interventions significantly reduce exacerbation frequency in appropriately selected individuals [81, 82].

Respiratory tract infections are also a major driver of inflammation in asthma, particularly in relation to seasonal peaks in asthma attacks. General measures such as influenza vaccination are commonly recommended, although they do not appear to greatly reduce exacerbation frequency and may be associated with an transient increase in wheeze in children [83]. No strategies have been robustly shown to reduce the risk of asthma attack associated with viral infections, although work is ongoing in this area. In the subset of individuals with asthma that are prone to bacterial infection and have predominantly neutrophilic inflammation, protracted treatment with immunomodulatory agents such as macrolides is under trial. Initial results suggest these may be effective although questions over their long-term consequences remain [84].

Assessing risk in primary care

A risk-based strategy is likely to require a substantial amount of baseline data and more extensive monitoring than simply using symptom questionnaires. It is perhaps best suited to a tertiary care setting for patients who can be characterised in detail. Such a strategy could lead to a reduction in admissions and unnecessary drug expenditure, and so be financially sustainable. It is less clear whether an effective risk-based strategy could be put into place for the majority of patients with asthma, although an initial pilot suggests technical hurdles would not restrict its use [85].

A compromise may be to set a trigger point at which patients are subject to a risk factor assessment and have their personalised management plan revised. As attacks are commonly defined by the need for oral corticosteroids, a prescription for prednisolone either in primary care or from an emergency department would appear a suitable prompt for such an assessment. This 'secondary prevention' approach would seek to address modifiable risk factors aggressively rather than waiting for attack frequency to increase.

Communicating risk

Practical aspects of communicating uncertainty

Once an individual's risk of an adverse asthma outcome is derived, the next challenge will be to convey that risk. To ensure precision and facilitate comparisons, numerical probabilities must be used and words such as 'doubtful' or 'likely' avoided [45]. As probabilities and natural frequencies can be misinterpreted [86, 87], they should be supported by graphs and text that contains comparisons and metaphors [88]. It is also necessary to clearly convey both the potential positive and negative

consequences of any changes. General recommendations for communicating risk are available [89].

Knowledge of risk and patient behaviour

Communicating information can facilitate shared decision-making and engage the patient with their chronic disease or risk factor management [90, 91]. In contrast, drug information leaflets are a good example of a discrepancy between information provided and information which patients find clear, valuable and useful [92].

The specific concept of risk in asthma does capture the attention of those with the disease; the online 'Triple A Test' saw over 50 000 completions after it appeared on the Asthma UK website and has now moved into a second iteration (accessible at www.asthma.org.uk). We speculate that efforts like this could encourage patients and clinicians to reappraise their ideas on risk in asthma, particularly around non-pharmacological interventions and understanding the consequences of acute attacks.

Where next?

Daily symptoms are important but are only one aspect of asthma. The main aim of asthma management and the prevailing concern of patients relates to asthma attacks. In this article, we have related the magnitude of this problem and discussed how asthma care might move towards a more explicit definition and management of an individual's risk of asthma attack. This appears to be a realistic aim, although there are key questions for the asthma community when considering further development:

- 1 What? Assessment and management of risk can occur at increasing levels of complexity with a diminishing return for each factor added. Should we aim for a simple rapid tool, or foreshadow developments in point of care testing and information technology and aim for something more comprehensive?
- 2 Who? Risk assessment tools and subsequent management strategies will need to be tailored in relation to patient factors (e.g. age, social and ethnic background) to be most effective. The central challenge here may be to coordinate common features between researchers developing such pathways.
- 3 Why? If a risk assessment tool is developed, we should be clear as to its aim so its impact can be appropriately assessed. Is it to reduce asthma attacks, admissions, intubations or death?
- 4 When? Any form of risk assessment will be heavily dependent on the resources available in the setting it is used. The time available to administer an assessment and the data to populate it will be different in

primary care, the emergency room and a tertiary clinic, as will the effects on health outcomes and expenditure.

- 5 How? Any assessment of risk and its impact on management needs to be communicated effectively to patients and other stakeholders. This may prove to be the most challenging aspect of the process.

Conclusion

The perceived stability of asthma management strategies over recent years may equally represent stagnation and perhaps tacit acceptance of suboptimal asthma management. Defining and managing risk in asthma is a strategy that offers potential in improving asthma

outcomes. Risk-based strategies are challenging to implement in terms of both their development and delivery but have the potential to improve health and economic outcomes. Adopting a secondary prevention strategy once a predetermined event has occurred (course of steroids/ hospital admission), with identification and aggressive treatment of modifiable risk factors, may drive future improvement in asthma care and reduce asthma attacks. This approach should be evaluated.

Conflict of interests

The authors declare no conflict of interest.

References

- 1 National Asthma Education and Prevention Program. Expert Panel Report 3 (EPR-3): guidelines for the diagnosis and management of asthma-summary report 2007. *J Allergy Clin Immunol* 2007; **120**(5 Suppl):S94–138.
- 2 Bousquet J, Mantzouranis E, Cruz AA *et al.* Uniform definition of asthma severity, control, and exacerbations: document presented for the World Health Organization Consultation on Severe Asthma. *J Allergy Clin Immunol* 2010; **126**:926–38.
- 3 Asher MI, Montefort S, Bjorksten B *et al.* Worldwide time trends in the prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and eczema in childhood: ISAAC Phases One and Three repeat multicountry cross-sectional surveys. *Lancet* 2006; **368**: 733–43.
- 4 NHS. The NHS Information Centre. Inpatient statistics, 2010–11. NHS, 2012. Available from: <http://www.hesonline.nhs.uk/Ease/servlet/ContentServer?siteID=1937&categoryID=202>.
- 5 Tata LJ, West J, Harrison T, Farrington P, Smith C, Hubbard R. Does influenza vaccination increase consultations, corticosteroid prescriptions, or exacerbations in subjects with asthma or chronic obstructive pulmonary disease? *Thorax* 2003; **58**:835–9.
- 6 Bai TR, Vonk JM, Postma DS, Boezen HM. Severe exacerbations predict excess lung function decline in asthma. *Eur Respir J* 2007; **30**:452–6.
- 7 James AL, Palmer LJ, Kicic E *et al.* Decline in lung function in the Busselton Health Study: the effects of asthma and cigarette smoking. *Am J Respir Crit Care Med* 2005; **171**:109–14.
- 8 Sears MR, Greene JM, Willan AR *et al.* A longitudinal, population-based, cohort study of childhood asthma followed to adulthood. *N Engl J Med* 2003; **349**:1414–22.
- 9 Mori H, Tanaka H, Ohno Y *et al.* Effect of intermittent systemic corticosteroid on bone metabolism in bronchial asthma patients. *J Asthma* 2009; **46**:142–6.
- 10 Cumming RG, Mitchell P. Inhaled corticosteroids and cataract: prevalence, prevention and management. *Drug Saf* 1999; **20**:77–84.
- 11 Thomas M, Bruton A, Moffat M, Cleland J. Asthma and psychological dysfunction. *Prim Care Respir J* 2011; **20**:250–6.
- 12 Health and Social Care Information Centre. Mortality from Asthma: Health and Social Care Information Centre, 2013.
- 13 Bahadori K, Doyle-Waters MM, Marra C *et al.* Economic burden of asthma: a systematic review. *BMC Pulm Med* 2009; **9**:24.
- 14 Anderson HR, Gupta R, Strachan DP, Limb ES. 50 years of asthma: UK trends from 1955 to 2004. *Thorax* 2007; **62**:85–90.
- 15 Wenzel S. Characteristics, definition and phenotypes of severe asthma. In: Chung KF, Bel E, Wenzel S, eds. *ERS monograph: difficult-to-treat severe asthma*. Vol. 51. European Respiratory Society, 2011.
- 16 British Thoracic Society and Scottish Intercollegiate Guidelines Network. British guideline on the management of asthma. *Thorax* 2008; **63**(Suppl. 4): iv1–121.
- 17 Bateman ED, Hurd SS, Barnes PJ *et al.* Global strategy for asthma management and prevention: GINA executive summary. *Eur Respir J* 2008; **31**:143–78.
- 18 Nathan RA, Sorkness CA, Kosinski M *et al.* Development of the asthma control test: a survey for assessing asthma control. *J Allergy Clin Immunol* 2004; **113**:59–65.
- 19 Juniper EF, O'Byrne PM, Guyatt GH, Ferrie PJ, King DR. Development and validation of a questionnaire to measure asthma control. *Eur Respir J* 1999; **14**:902–7.
- 20 Blakey JD, Woolnough K, Fellows J, Walker S, Thomas M, Pavord ID. Assessing the risk of attack in the management of asthma: a review and proposal for revision of the current control-centred paradigm. *Prim Care Respir J* 2013; **22**:344–52.
- 21 Pavord I. Complex airway disease: an approach to assessment and management. *Lancet Respir Med* 2012; **1**:84–90.
- 22 Griffiths C, Clark N. Predicting the risk of an asthma attack: the way ahead? *Prim Care Respir J* 2012; **21**:368–70.
- 23 Edwards W. The theory of decision making. *Psychol Bull* 1954; **51**:380–417.
- 24 Hall KH. Reviewing intuitive decision-making and uncertainty: the implications for medical education. *Med Educ* 2002; **36**:216–24.
- 25 Slovic P. Perception of risk. *Science* 1987; **236**:280–5.

- 26 Hertwig R, Pachur T, Kurzenhauser S. Judgments of risk frequencies: tests of possible cognitive mechanisms. *J Exp Psychol Learn Mem Cogn* 2005; 31:621–42.
- 27 Lichtenstein S, Slovic P, Fischhoff B, Layman M, Combs B. Judged frequency of lethal events. *J Exp Psychol Hum Learn* 1978; 4:551–78.
- 28 Spiegelhalter D. Micromorts. Available from: <http://understandinguncertainty.org/micromorts2012>.
- 29 Reddel HK, Taylor DR, Bateman ED *et al.* An official American Thoracic Society/European Respiratory Society statement: asthma control and exacerbations: standardizing endpoints for clinical asthma trials and clinical practice. *Am J Respir Crit Care Med* 2009; 180:59–99.
- 30 Thomas M, Gruffydd-Jones K, Stonham C, Ward S, Macfarlane TV. Assessing asthma control in routine clinical practice: use of the Royal College of Physicians '3 questions'. *Prim Care Respir J* 2009; 18:83–8.
- 31 Volbeda F, Broekema M, Lodewijk ME *et al.* Clinical control of asthma associates with measures of airway inflammation. *Thorax* 2013; 68:19–24.
- 32 Meltzer EO, Busse WW, Wenzel SE *et al.* Use of the Asthma Control Questionnaire to predict future risk of asthma exacerbation. *J Allergy Clin Immunol* 2011; 127:167–72.
- 33 Peters D, Chen C, Markson LE, Allen-Ramey FC, Vollmer WM. Using an asthma control questionnaire and administrative data to predict health-care utilization. *Chest* 2006; 129:918–24.
- 34 Buhl R, O'Byrne P, Humber M, Peterson S, Eriksson G. Patient baseline variables predict future asthma control status and risk of exacerbations. European Respiratory Society Annual Congress, 2010.
- 35 Lotvall J, Akdis CA, Bacharier LB *et al.* Asthma endotypes: a new approach to classification of disease entities within the asthma syndrome. *J Allergy Clin Immunol* 2011; 127:355–60.
- 36 Haldar P, Pavord ID, Shaw DE *et al.* Cluster analysis and clinical asthma phenotypes. *Am J Respir Crit Care Med* 2008; 178:218–24.
- 37 Feldman JM, Kutner H, Matte L *et al.* Prediction of peak flow values followed by feedback improves perception of lung function and adherence to inhaled corticosteroids in children with asthma. *Thorax* 2012; 67:1040–5.
- 38 Gonem S, Raj V, Wardlaw AJ, Pavord ID, Green R, Siddiqui S. Phenotyping airways disease: an A to E approach. *Clin Exp Allergy* 2012; 42:1664–83.
- 39 Bateman ED, Reddel HK, Eriksson G *et al.* Overall asthma control: the relationship between current control and future risk. *J Allergy Clin Immunol* 2010; 125:600–8, 8 e1–8 e6.
- 40 Blakey JD, Wardlaw AJ. What is severe asthma? *Clin Exp Allergy* 2012; 42:617–24.
- 41 Romagnoli M, Caramori G, Braccioni F *et al.* Near-fatal asthma phenotype in the ENFUMOSA Cohort. *Clin Exp Allergy* 2007; 37:552–7.
- 42 Miller MK, Lee JH, Blanc PD *et al.* TENOR risk score predicts healthcare in adults with severe or difficult-to-treat asthma. *Eur Respir J* 2006; 28:1145–55.
- 43 Shaw D, Green R, Berry M *et al.* A cross-sectional study of patterns of airway dysfunction, symptoms and morbidity in primary care asthma. *Prim Care Respir J* 2012; 21:283–7.
- 44 Lucas AE, Smeenk FW, Smelee IJ, van Schayck CP. Overtreatment with inhaled corticosteroids and diagnostic problems in primary care patients, an exploratory study. *Fam Pract* 2008; 25:86–91.
- 45 Dennis S, Price JF, Vickers M, Frost CD, Levy ML, Barnes PJ. The management of newly identified asthma in primary care in England. *Prim Care Respir J* 2002; 11:120–2.
- 46 Robinson DS, Campbell DA, Durham SR, Pfeffer J, Barnes PJ, Chung KF. Systematic assessment of difficult-to-treat asthma. *Eur Respir J* 2003; 22:478–83.
- 47 Boulet LP, Franssen E. Influence of obesity on response to fluticasone with or without salmeterol in moderate asthma. *Respir Med* 2007; 101:2240–7.
- 48 Yoon R, McKenzie DK, Bauman A, Miles DA. Controlled trial evaluation of an asthma education programme for adults. *Thorax* 1993; 48:1110–6.
- 49 Ni Chroinin M, Lasserson TJ, Greenstone I, Ducharme FM. Addition of long-acting beta-agonists to inhaled corticosteroids for chronic asthma in children. *Cochrane Database Syst Rev* 2009; CD007949.
- 50 Pauwels RA, Lofdahl CG, Postma DS *et al.* Effect of inhaled formoterol and budesonide on exacerbations of asthma. Formoterol and Corticosteroids Establishing Therapy (FACET) International Study Group. *N Engl J Med* 1997; 337:1405–11.
- 51 Bateman ED, Boushey HA, Bousquet J *et al.* Can guideline-defined asthma control be achieved? The Gaining Optimal Asthma Control study. *Am J Respir Crit Care Med* 2004; 170:836–44.
- 52 Rank MA, Hagan JB, Park MA *et al.* The risk of asthma exacerbation after stopping low-dose inhaled corticosteroids: a systematic review and meta-analysis of randomized controlled trials. *J Allergy Clin Immunol* 2013; 131:724–9.
- 53 Price D, Haughney J, Sims E *et al.* Effectiveness of inhaler types for real-world asthma management: retrospective observational study using the GPRD. *J Asthma Allergy* 2011; 4:37–47.
- 54 de Vries F, Setakis E, Zhang B, van Staa TP. Long-acting β_2 -agonists in adult asthma and the pattern of risk of death and severe asthma outcomes: a study using the GPRD. *Eur Respir J* 2010; 36:494–502.
- 55 Olesen JB, Lip GY, Hansen ML *et al.* Validation of risk stratification schemes for predicting stroke and thromboembolism in patients with atrial fibrillation: nationwide cohort study. *BMJ* 2011; 342:d124.
- 56 Schmidt M, Jacobsen JB, Lash TL, Botker HE, Sorensen HT. 25 year trends in first time hospitalisation for acute myocardial infarction, subsequent short and long term mortality, and the prognostic impact of sex and comorbidity: a Danish nationwide cohort study. *BMJ* 2012; 344:e356.
- 57 Smolina K, Wright FL, Rayner M, Goldacre MJ. Determinants of the decline in mortality from acute myocardial infarction in England between 2002 and 2010: linked national database study. *BMJ* 2012; 344:d8059.
- 58 Skyler JS, Lasky IA, Skyler DL, Robertson EG, Mintz DH. Home blood glucose monitoring as an aid in diabetes management. *Diabetes Care* 1978; 1:150–7.
- 59 Lockhart W, Smith DH, Mair A, Wilson WA. Practical experience with the

- peak flow meter. *Br Med J* 1960; 1:37–8.
- 60 Brown HM. Treatment of chronic asthma with prednisolone. Significance of eosinophils in the sputum. *Lancet* 1958; 2:1245–7.
 - 61 Flood-Page P, Swenson C, Faiferman I *et al.* A study to evaluate safety and efficacy of mepolizumab in patients with moderate persistent asthma. *Am J Respir Crit Care Med* 2007; 176:1062–71.
 - 62 Pavord ID, Korn S, Howarth P *et al.* Mepolizumab for severe eosinophilic asthma (DREAM): a multicentre, double-blind, placebo-controlled trial. *Lancet* 2012; 380:651–9.
 - 63 Seddon P, Bara A, Ducharme FM, Lasserson TJ. Oral xanthines as maintenance treatment for asthma in children. *Cochrane Database Syst Rev* 2006;CD002885.
 - 64 Castro M, Rubin AS, Laviolette M *et al.* Effectiveness and safety of bronchial thermoplasty in the treatment of severe asthma: a multicenter, randomized, double-blind, sham-controlled clinical trial. *Am J Respir Crit Care Med* 2010; 181:116–24.
 - 65 Blakey JD, Hall IP. Current progress in pharmacogenetics. *Br J Clin Pharmacol* 2011; 71:824–31.
 - 66 Wechsler ME, Castro M, Lehman E *et al.* Impact of race on asthma treatment failures in the asthma clinical research network. *Am J Respir Crit Care Med* 2011; 184:1247–53.
 - 67 Jatakanon A, Lim S, Barnes PJ. Changes in sputum eosinophils predict loss of asthma control. *Am J Respir Crit Care Med* 2000; 161:64–72.
 - 68 Leuppi JD, Salome CM, Jenkins CR *et al.* Predictive markers of asthma exacerbation during stepwise dose reduction of inhaled corticosteroids. *Am J Respir Crit Care Med* 2001; 163:406–12.
 - 69 Pizzichini MM, Pizzichini E, Clelland L *et al.* Prednisone-dependent asthma: inflammatory indices in induced sputum. *Eur Respir J* 1999; 13:15–21.
 - 70 Patsky HL, Cates CJ, Lasserson TJ *et al.* A systematic review and meta-analysis: tailoring asthma treatment on eosinophilic markers (exhaled nitric oxide or sputum eosinophils). *Thorax* 2012; 67:199–208.
 - 71 Green RH, Brightling CE, McKenna S *et al.* Asthma exacerbations and sputum eosinophil counts: a randomised controlled trial. *Lancet* 2002; 360: 1715–21.
 - 72 Patsky HL, Cates CJ, Li A, Kynaston JA, Turner C, Chang AB. Tailored interventions based on exhaled nitric oxide versus clinical symptoms for asthma in children and adults. *Cochrane Database Syst Rev* (Online) 2009; CD006340.
 - 73 Powell H, Murphy VE, Taylor DR *et al.* Management of asthma in pregnancy guided by measurement of fraction of exhaled nitric oxide: a double-blind, randomised controlled trial. *Lancet* 2011; 378:983–90.
 - 74 Shaw DE, Berry MA, Thomas M *et al.* The use of exhaled nitric oxide to guide asthma management: a randomized controlled trial. *Am J Respir Crit Care Med* 2007; 176:231–7.
 - 75 Bafadhel M, McKenna S, Terry S *et al.* Blood eosinophils to direct corticosteroid treatment of exacerbations of chronic obstructive pulmonary disease: a randomized placebo-controlled trial. *Am J Respir Crit Care Med* 2012; 186:48–55.
 - 76 Boudier A, Curjuric I, Basagana X *et al.* Ten-year follow-up of cluster-based asthma phenotypes in adults. A pooled analysis of three cohorts. *Am J Respir Crit Care Med* 2013; 188:550–60.
 - 77 Wenzel S, Ford L, Pearlman D *et al.* Dupilumab in persistent asthma with elevated eosinophil levels. *N Engl J Med* 2013; 368:2455–66.
 - 78 Corren J, Lemanske RF, Hanania NA *et al.* Lebrikizumab treatment in adults with asthma. *N Engl J Med* 2011; 365:1088–98.
 - 79 Gotzsche PC, Johansen HK. House dust mite control measures for asthma. *Cochrane Database Syst Rev* 2008;CD001187.
 - 80 Boyle RJ, Pedroletti C, Wickman M *et al.* Nocturnal temperature controlled laminar airflow for treating atopic asthma: a randomised controlled trial. *Thorax* 2012; 67:215–21.
 - 81 Norman G, Faria FR, Paton F *et al.* Omalizumab for the treatment of severe persistent allergic asthma: a systematic review and economic evaluation. *J Health Technol Assess* 2013; 17:1–342.
 - 82 Abramson MJ, Puy RM, Weiner JM. Injection allergen immunotherapy for asthma. *Cochrane Database Syst Rev* 2010;CD001186.
 - 83 Cates CJ, Jefferson TO, Rowe BH. Vaccines for preventing influenza in people with asthma. *Cochrane Database Syst Rev* 2008;CD000364.
 - 84 Brusselle GG, Vanderstichele C, Jordens P *et al.* Azithromycin for prevention of exacerbations in severe asthma (AZISAST): a multicentre randomised double-blind placebo-controlled trial. *Thorax* 2013; 68:322–9.
 - 85 Smith JR, Noble MJ, Musgrave S *et al.* The at-risk registers in severe asthma (ARRISA) study: a cluster-randomised controlled trial examining effectiveness and costs in primary care. *Thorax* 2012; 67:1052–60.
 - 86 Galesic M, Garcia-Retamero R. Statistical numeracy for health: a cross-cultural comparison with probabilistic national samples. *Arch Intern Med* 2010; 170:462–8.
 - 87 Woloshin S, Schwartz LM. Communicating data about the benefits and harms of treatment: a randomized trial. *Ann Intern Med* 2011; 155:87–96.
 - 88 Paling J. Strategies to help patients understand risks. *BMJ* 2003; 327: 745–8.
 - 89 Spiegelhalter D, Pearson M, Short I. Visualizing uncertainty about the future. *Science* 2011; 333:1393–400.
 - 90 Parkes G, Greenhalgh T, Griffin M, Dent R. Effect on smoking quit rate of telling patients their lung age: the Step2quit randomised controlled trial. *BMJ* 2008; 336:598.
 - 91 Schmalings KB, Blume A, Afari N. A randomized controlled pilot study of motivational interviewing to change attitudes about adherence to medications for asthma. *J Clin Psychol Med Settings* 2001; 8:167–72.
 - 92 Raynor DK, Blenkinsopp A, Knapp P *et al.* A systematic review of quantitative and qualitative research on the role and effectiveness of written information available to patients about individual medicines. *Health Technol Assess* 2007; 11:iii, 1–160.
 - 93 Dennis SM, Altmann DR, Lee TH. Increase in daytime symptoms is a sensitive and specific criterion for predicting corticosteroid-treated exacerbations in a clinical asthma trial. *Clin Exp Allergy* 2005; 35:308–12.
 - 94 Lehtimäki L, Kankaanranta H, Saarelainen S, Turjanmaa V, Moilanen E. Increased alveolar nitric oxide concentration in asthmatic patients with

- nocturnal symptoms. *Eur Respir J* 2002; 20:841–5.
- 95 Skobeloff EM, Spivey WH, St Clair SS, Schoffstall JM. The influence of age and sex on asthma admissions. *JAMA* 1992; 268:3437–40.
- 96 Bousquet J, Gaugris S, Kocavar VS *et al.* Increased risk of asthma attacks and emergency visits among asthma patients with allergic rhinitis: a subgroup analysis of the investigation of montelukast as a partner agent for complementary therapy [corrected]. *Clin Exp Allergy* 2005; 35:723–7.
- 97 Chilmonczyk BA, Salmun LM, Megathlin KN *et al.* Association between exposure to environmental tobacco smoke and exacerbations of asthma in children. *N Engl J Med* 1993; 328:1665–9.
- 98 Lee SL, Wong WH, Lau YL. Association between air pollution and asthma admission among children in Hong Kong. *Clin Exp Allergy* 2006; 36: 1138–46.
- 99 Williams LK, Peterson EL, Wells K *et al.* Quantifying the proportion of severe asthma exacerbations attributable to inhaled corticosteroid nonadherence. *J Allergy Clin Immunol* 2011; 128:1185–91 e2.
- 100 Naureckas ET, Dukic V, Bao X, Rathouz P. Short-acting beta-agonist prescription fills as a marker for asthma morbidity. *Chest* 2005; 128:602–8.
- 101 Bacon SL, Bouchard A, Loucks EB, Lavoie KL. Individual-level socioeconomic status is associated with worse asthma morbidity in patients with asthma. *Respir Res* 2009; 10:125.
- 102 Sandberg S, Paton JY, Ahola S *et al.* The role of acute and chronic stress in asthma attacks in children. *Lancet* 2000; 356:982–7.
- 103 Cowie RL, Revitt SG, Underwood MF, Field SK. The effect of a peak flow-based action plan in the prevention of exacerbations of asthma. *Chest* 1997; 112:1534–8.
- 104 Fuhlbrigge AL, Weiss ST, Kuntz KM, Paltiel AD. Forced expiratory volume in 1 second percentage improves the classification of severity among children with asthma. *Pediatrics* 2006; 118:e347–55.
- 105 Stenius-Aarniala B, Poussa T, Kvarnstrom J, Gronlund EL, Ylikahri M, Mustajoki P. Immediate and long term effects of weight reduction in obese people with asthma: randomised controlled study. *BMJ* 2000; 320:827–32.
- 106 Magadle R, Berar-Yanay N, Weiner P. The risk of hospitalization and near-fatal and fatal asthma in relation to the perception of dyspnea. *Chest* 2002; 121:329–33.