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CLINICAL REVIEW

# Assessing the risk of attack in the management of asthma: a review and proposal for revision of the current control-centred paradigm

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**Abstract**

Asthma guidelines focus on day-to-day control of symptoms. However, asthma attacks remain common. They continue to cause mortality and considerable morbidity, and are a major financial burden to the UK National Health Service (NHS) and the wider community. Asthma attacks have chronic consequences, being associated with loss of lung function and significant psychological morbidity. In this article we argue that addressing daily symptom control is only one aspect of asthma treatment, and that there should be a more explicit focus on reducing the risk of asthma attacks. Management of future risk by general practitioners is already central to other conditions such as ischaemic heart disease and chronic renal impairment. We therefore propose a revised approach that separately considers the related domains of daily control and future risk of asthma attack. We believe this approach will have advantages over the current 'stepwise' approach to asthma management. It should encourage individualised treatment, including non-pharmacological measures, and thus may lead to more efficacious and less harmful management strategies. We speculate that this type of approach has the potential to reduce morbidity and healthcare costs related to asthma attacks.


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## Asthma attacks

### Asthma attacks remain common

Asthma is a complex syndrome with a spectrum of presentations and clinical courses.[1-6] However, in all asthma subtypes and at any age[7-9] there is the potential for a subacute or abrupt deterioration in both symptom control and objective measures of airflow obstruction. This situation is referred to as an asthma exacerbation or asthma attack.[10] We prefer the term 'asthma attack' as it seems better understood by those outside medicine and more clearly conveys the potential seriousness of the episode.[11] Asthma attacks are common,[12,13] accounting for almost 90,000 admissions per annum in the UK[14] and many more consultations in general practice.[15,16] It is notable that they no longer appear to be reducing in frequency,[17] and their treatment has changed little in the past 20 years.

### Asthma attacks have serious consequences

Asthma attacks are associated with substantial morbidity, not only in terms of respiratory disease and general debility from critical illness but also through the adverse effects caused by medications.[18,19] The abrupt decline in physical functioning and risk of serious complications during attacks results in asthma being a significant source of anxiety and panic.[20-24]

An underappreciated aspect of asthma attacks is that they are associated with worsening lung function. Children with a history of asthma attacks have lung function deficits compared with their

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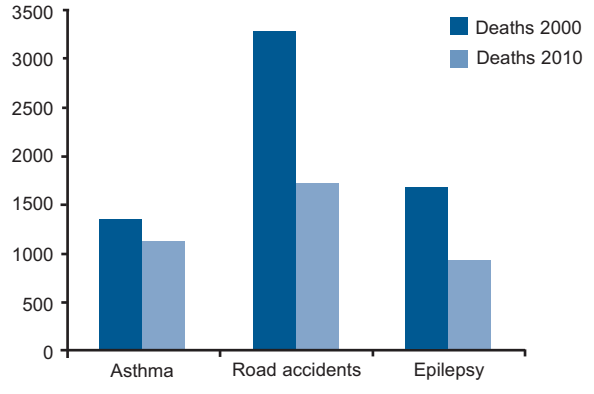
peers[25,26] that persist and often worsen into adult life.[27,28] For example, of the 1,000 children enrolled into the Childhood Asthma Management Program (CAMP), one-third had had spirometric airflow obstruction when assessed at age 6–8 years, and this proportion increased to more than half by age 18.[29] Early intervention with inhaled corticosteroids appears to protect against this decline.[30,31] A cohort study examining the effect of severe asthma attacks on lung function in adults found that attack frequency was closely correlated with loss of lung function: the loss of lung function in individuals experiencing one asthma attack per year was equivalent to that seen in individuals who smoke 20 cigarettes per day.[32] It appears that the degree of deficit is associated with airway inflammation,[33] although this relationship is complex.[34] Crucially, it appears that any decline associated with asthma attacks may be ameliorated with appropriate therapy.[31,35] It may be that measurements other than simple spirometry will prove more informative in elucidating the relationship between lung function and airway inflammation.[36,37]

Asthma also continues to be a significant cause of mortality. The number of asthma-related deaths has been slower to fall than for other largely preventable causes of death: almost as many people are recorded as dying from asthma each year as from road accidents in the UK (Figure 1). Although the true number of asthma-related deaths may well be lower than official figures suggest,[38] the trend in these statistics remains worrying and has led to the recent launch of a national UK review which will report soon (http://www.rcplondon.ac.uk/projects/national-review-asthma-deaths).

The frequency and potential seriousness of asthma attacks results in considerable direct healthcare costs.[39,40] In addition, there are the social and economic consequences of a temporary reduction in functioning of a usually healthy adult or of adults caring for an acutely unwell child.[41]

Asthma attacks therefore lead to substantial morbidity and mortality with substantial indirect and direct economic costs. Before considering how this might be addressed, we will discuss how asthma attacks relate to two commonly considered dimensions of asthma: severity and control.

**Figure 1. Deaths from asthma, road accidents, and epilepsy in 2000 and 2010. Data from UK National Statistics and the Department for Transport**




# Control, severity and risk

## Asthma control and asthma attacks

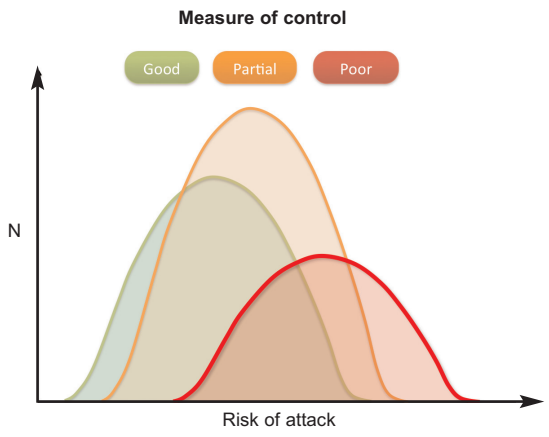
Several validated questionnaires of daily symptom control in asthma are in common use, such as the Asthma Control Test (ACT),[42] the Asthma Control Questionnaire (ACQ),[43] and the Royal College of Physicians 'Three Questions'.[44] This is unsurprising as monitoring and improving daily symptom control is the focus of current international guidelines. It may seem that assessing daily control is sufficient to assess the risk of asthma attack. Indeed, poor scores on these instruments are associated with asthma attack frequency in study populations.[45-47] However, their predictive value for an individual appears limited: area under receiver operator curve (ROC) values have been less than 0.7 for exacerbation outcomes.[45] This poor performance stems from daily control and future risk being related but separate entities. This difference is demonstrated by serial peak expiratory flow (PEF) monitoring. The high degree of PEF variability and large bronchodilator response seen with poor daily control contrasts with reduced PEF variability (around a low value) and loss of bronchodilator response leading up to an asthma attack.[48] It is also uncertain over how long daily control must be present in order to have a significant impact on future risk. Furthermore, simple control questionnaires do not put current control in the context of information that would usually be incorporated into an experienced practitioner's assessment of a patient with asthma.[49] For example, retrospective analyses of large datasets have found factors such as (but not solely) smoking status, current medication, forced expiratory volume in one second ($FEV_1$) as a percentage of predicted, blood eosinophil count, and previous healthcare use to be predictors of poor outcomes and emergency healthcare use.[50-52] These issues lead us to consider asthma severity.

## Asthma severity and asthma attacks

A significant minority of individuals with asthma have persisting daily symptoms or demonstrable airways inflammation despite compliance with potent inhaled steroids and long-acting $\beta_2$-agonists.[53,54] These patients have more severe asthma, but may attain significantly better control with additional asthma therapies, treatment of comorbidity and support.[55-59] Equally, patients with very poorly controlled disease on suboptimal therapy may become symptom-free with the use of a single regular inhaler.[60] Such findings have led to a greater clinical focus on the separation of the domains of asthma severity and control following the earlier recognition of their differing pathophysiology and expression.[61,62]

Although asthma severity is associated with the risk of asthma attack, it is again not predictive: data from the European Network for Understanding Mechanisms of Severe Asthma (ENFUMOSA) found that patients with a history of near-fatal asthma in the past 5 years could not be reliably distinguished from those with mild to moderate asthma in stable conditions using common measures of asthma severity.[63] The Epidemiology and Natural History of Asthma: Outcomes and Treatment Regimens (TENOR) study sought a multivariable score associated with the prospective risk of requiring hospitalisation or an emergency department visit related to asthma. Although the list of potentially informative variables in the analysis included common aspects of severe asthma definitions such as daily

**Figure 2. Schematic to illustrate the risk of asthma attack for populations of asthma patients with good, partial, and poor asthma control**




control questionnaires, inhaled or regular oral steroid use, and use of other controller medication, many such factors did not feature in the final model.[64] This more inclusive approach also begins to highlight factors that are robustly associated with asthma attacks but are not captured by current questionnaires such as tobacco smoke exposure,[65-67] non-concordance,[68,69] socio-economic status,[70,71] atopy, and upper airways disease,[72-74] persistent eosinophilic airway inflammation (see above) and adiposity.[75,76]

The risk of asthma attack therefore appears to be closely associated with disease severity and daily symptom control but is not fully described by them (Figure 2). Although statements and guidelines from learned institutions advocate that patient assessments should incorporate elements of current control and future risk, it is not clear how this latter aspect is accomplished. As future risk is not emphasised in these documents to the same degree as daily control, it is also unclear how commonly risk assessment is undertaken in routine practice.

## Phenotyping and deconstruction

The heterogeneity of asthma of all severities has been highlighted and explored in widely read and cited papers (e.g. Haldar *et al*.[9]). This clinical variation is related to key underlying pathophysiological processes.[77] On this background and with the evident heterogeneity in other airways disease,[78] there has been a recent emphasis on the limitations of current nomenclature. A universal 'one size fits all' approach risks applying confusing or misleading labels – particularly when there is diagnostic uncertainty – and thus exposing patients to unnecessary therapy. For example, patients with a seemingly robust label of chronic obstructive pulmonary disease (COPD) may have exacerbations driven by eosinophilic inflammation, and those who do not have their recovery impaired by indiscriminate use of oral steroids.[79,80] The key feature is therefore not the label of COPD but choosing appropriate treatment based on the type of inflammation occurring.

It would therefore appear that deconstructing airways diseases into their component abnormalities may be a more productive tactic than adhering to traditional labels,[81] at least for those who respond suboptimally to first-line treatment. Poor daily symptom control can be driven by one or more of a number of processes which require very different treatments, such as significant airway hyper-responsiveness, heightened cough reflex, damaged airways, or dysfunctional breathing. By applying approaches such as the 'A to E' system (see Table 1), a clinician could be freed to identify which interventions will benefit the individual patient who faces them and which tests should be used for assessment and monitoring. We await with interest the outcomes of controlled assessments of such approaches.

### Risk of asthma attack and components of airways disease

The relative contribution of the aforementioned pathophysiological

**Table 1. The A to E of airways disease: a proposal for deconstructing complex airways disease to facilitate assessment and treatment[81]**

| | Component | Clinical features | Test results |
|---|---|---|---|
| A | Airways hyper-responsiveness | Short-term variable breathlessness and wheeze | Methacholine challenge positive<br>>12% bronchodilator response<br>>20% PEFR variability in 24 hrs |
| B | Bronchitis | May be none<br>Subacute marked deteriorations<br>Morning productive cough | Raised induced sputum cell count<br>Potentially high FeNO<br>Otherwise unexplained blood eosinophilia |
| C | Cough reflex hypersensitivity | Dry cough in relation to temperature change, talking, laughing | Excessive response to inhaled tussive stimuli (e.g. capsaicin) |
| D | Damage | Fixed limitation in exercise due to breathlessness | Fixed airflow obstruction<br>Impaired gas transfer<br>Emphysema or bronchiectasis on CT scan |
| E | Extrapulmonary co-morbidity | Obesity, rhinitis, vocal cord dysfunction | Dependent on nature of co-morbidity |

FeNO=fractional exhaled nitric oxide, PEFR=peak expiratory flow rate.

processes are related to an individual's risk of an asthma attack.[82] Uncontrolled eosinophilic bronchitis in asthma may lead to few daily symptoms but a high rate of asthma attack.[9,83] This pattern is often seen in older men with late-onset asthma.[9] Controlling such inflammation results in a significant reduction in asthma attacks.[84] Similarly, people with frequent asthma symptoms may not have a great deal of inflammation.[9,83] Such individuals (typically obese females, in our experience) are often unnecessarily exposed to significant quantities of corticosteroid therapy despite their low risk of a serious asthma attack; this treatment may worsen obesity and delay the introduction of a more appropriate treatment regimen. Individuals whose symptoms are driven by dysfunctional breathing rather than airways hyper-reactivity represent a more extreme disconnection between symptoms and risk. Again, the effects from oral corticosteroids and frequent $\beta_2$-agonist inhalation may worsen the clinical picture. The disparity between symptoms (perceived control) and objective measures of disease might therefore be an important reason why the current symptom-guided management approach fails in some patients.

The preceding observations have largely been made in a tertiary referral setting with access to induced sputum cell counts, although the principles are likely to apply to those treated in other settings. Although differential sputum cell counts are valuable, they are time-consuming and need specialist facilities. Over-reliance on a single test such as sputum or blood eosinophilia also risks neglecting individuals at risk of attacks driven by infection or other exposures, co-morbidity, and genetic susceptibility.

Psychosocial factors require consideration when assessing the risk of asthma attack. For example, individuals who have great confidence in their own ability to manage their disease may be more likely to be non-concordant with treatment and delay seeking help when deterioration occurs. Such repressive (or 'denial coping') coping strategies[85] have been found to be more common in those with near-fatal asthma attacks,[86,87] as well as being associated with a greater symptom burden[88] and worse lung function.[89] Individual perceptions of risk of disease and treatment will also depend on circumstances, experiences, and understanding. These individual perceptions may be modified through education and shared decision-making, and these are discussed in a later section.

## Risk and treatment

### Asthma therapies do not affect risk and control equally

For many people with asthma, the stepwise prescription of treatment to reduce daily symptoms will be appropriate to reduce their risk of attacks. However, for the significant proportion of individuals who have discordant daily symptoms and future risk, this will not be the case: as noted, it may result in excessive therapy for those with frequent symptoms and a low risk of asthma attack, and inadequate intervention for those with fewer symptoms but who are at higher risk. The heterogeneity in clinical asthma would be a lesser issue if available interventions had an equal effect on daily symptoms and risk of acute deterioration. Under those circumstances, the current straightforward stepwise approach would be valid for almost all patients.[90]

Available treatments for asthma are, however, unequal in their benefit. Xanthines, for example, improve daily symptoms but do not affect the risk of an asthma attack.[91] When high-dose inhaled steroids are compared with lower dose steroids/long-acting $\beta_2$-agonist combination therapy, the former leads to a greater reduction in asthma attacks whereas the latter has more effect on symptom scores.[92] This discrepancy in effect is also apparent for newer and more costly therapies such as laminar airflow units for severe atopic asthma,[93] bronchial thermoplasty for persistent airways hyper-responsiveness,[94] and monoclonal antibody therapy for persistent eosinophilic inflammation.[95] This latter therapy is a key example of the need to consider risk and control separately: mepolizumab (anti-IL-5) was found to be ineffective in initial studies[96] including people with asthma selected by (commonly applied) criteria of symptoms and bronchial hyper-reactivity. It has subsequently been shown to halve the risk of an asthma attack in individuals who are at high risk, as reflected by eosinophilic inflammation, fixed airflow obstruction, and multiple previous asthma attacks.[95,97,98] Strikingly, the beneficial effects of treatment appear to be least in patients with a large acute bronchodilator response.

It is widely accepted that high-cost specialist interventions such as those mentioned above require a fuller assessment of an individual's asthma in a tertiary referral centre. This should avoid the temptation to try the next new therapy for an individual with difficult asthma and give the greatest opportunity for these interventions to prove successful and financially sustainable. However, we should not overlook the need for appropriate assessment before commencing more commonplace therapies: treatments such as inhaled corticosteroids,[99] long-acting $\beta_2$-agonists,[100] xanthines,[91] and potentially long-acting anticholinergics[101] may carry a risk of significant adverse events. Some of these common therapies are also costly; for example, they account for greater healthcare expenditure than admissions, even in severe asthma.[102] Drug costs are also inflated as clinicians are slow to reduce or withdraw drugs that have equivocal additional benefit.[103] These costs are increasingly important in the UK NHS and are a major barrier to delivering care in developing countries. The number of long-acting bronchodilators and combination products on the horizon is likely to further complicate this picture.[104-107]

### The stepwise approach focuses on drug treatment

The focus on treatment 'steps' in guidelines draws the user into escalating drug therapy for asthma symptoms. The resultant narrow approach may distract from other informative sections and the major benefits that can be gained from interventions such as education, weight loss and exercise, and smoking cessation programmes. In particular, stepwise management does not readily accommodate interventions requiring multidisciplinary expertise rather than a prescription. We acknowledge that aspects of asthma management such as concordance reviews with pharmacists or specialist nurses, dysfunctional breathing treatment from physiotherapists, clinical psychology input, and speech therapy assessment of vocal cord dysfunction are contained within guidance but we contend that they are not sufficiently emphasised or contextualised. The effect of

**Table 2. Interventions for asthma and indication of their likely effect on daily control and risk of severe asthma attack**

| Intervention | Daily control | Risk reduction |
|---|---|---|
| Long-acting beta-agonists (alone) | ++ | – |
| Anticholinergics | ++ | + |
| Corticosteroids | + | ++ |
| Montelukast | + | + |
| Theophylline | + | 0 |
| Weight loss | ++ | + |
| Concordance review | + | ++ |
| Smoking cessation programme | ++ | ++ |
| Physiotherapy review | ++ | 0 |
| Bronchial thermoplasty | ++ | + |
| Mepolizumab | 0 | ++ |

++=major beneficial effect, +=some beneficial effect, 0=no effect, –=worsens.

therapeutic interventions on asthma control and risk of attack is summarised in Table 2. Engaging with the various perspectives of those involved in a multidisciplinary team also affords the opportunity to better assess patient attitudes and perceptions.[108] This information enables healthcare providers to challenge the assumptions of a stepwise model such as consistency and accuracy in the patient's history, a clear understanding by the patient of the treatment intended, that treatment is taken as intended, and that all patients wish to obtain the best level of health possible. We would recommend that costly treatments or those with potentially serious adverse effects are only commenced after a multidisciplinary team review.

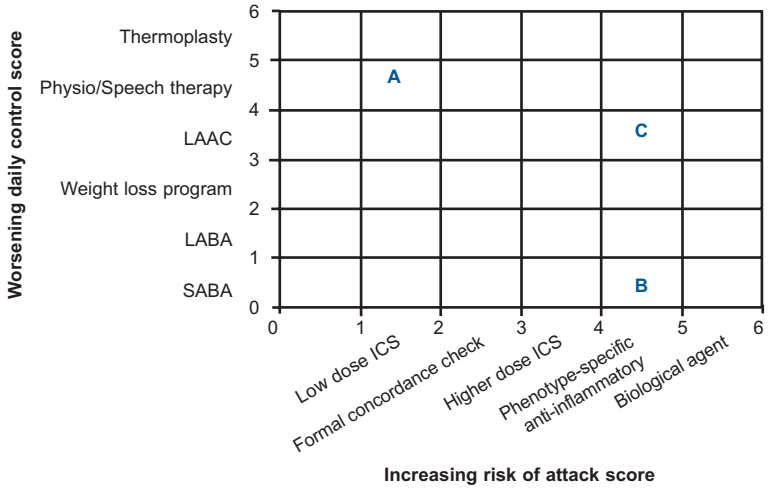
## Assessing both risk and control

We have discussed the importance of risk as an additional consideration to daily control, and of the unequal effects of available interventions on these dimensions. It would therefore be helpful to have a simple way of assessing risk in an individual with asthma. Pilot studies suggest that the creation of such a simple risk assessment score is feasible.[109] The tens of thousands of completions of the Asthma UK 'triple A' (Avoiding Asthma Attacks) test suggest that such scores may successfully engage users,[110] and feedback from this test suggests it could effect favourable behavioural change. Research in this area is ongoing,[111] and it is likely that risk assessment scores (with and without biomarker measurement) will be forthcoming in the near future. Explicit risk assessment could be the missing piece that has the potential to facilitate more effective treatment, which could also be cheaper if inappropriate treatment is reduced.

We believe that future asthma guidelines should consider including explicit assessments of risk and control rather than simply discussing factors related to the risk of attack. These assessments could then inform appropriate interventions. An example of a 'co-ordinates' system is shown in Figure 3. Under such a scheme, risk and control are assessed independently. Interventions for risk and control dimensions are then augmented or reduced along the relevant axes. In Figure 3, patient A has poor control but few risk factors. Use of this new approach increases the likelihood of gaining control but does not expose the patient to unnecessary parenteral steroids as would be the case following existing guidelines. In patient B the risk of severe attack is addressed, which would otherwise have been overlooked. Patient C has treatment tailored to his/her specific risk factor. We acknowledge that all patients should have their

**Figure 3. (A) An example of the proposed coordinates system to inform asthma management. Ongoing poor daily control results in escalation along the y axis and ongoing risk of severe asthma attack leads to escalation along the x axis. LAAC=long-acting anticholinergic, LABA=long-acting $\beta_2$-agonist, SABA=short-acting $\beta_2$-agonist, ICS=inhaled corticosteroid. Phenotype-specific anti-inflammatory relates to oral treatment (e.g. prednisolone or macrolide). The letters on the chart relate to example patients and are discussed in the text and panel (B). (B) Treatment received by example patients A, B, and C under existing and proposed guideline structures. Patient identifying letters relate to panel (A). Smoking cessation advice is not explicitly included above but is evidently a key aspect of management**

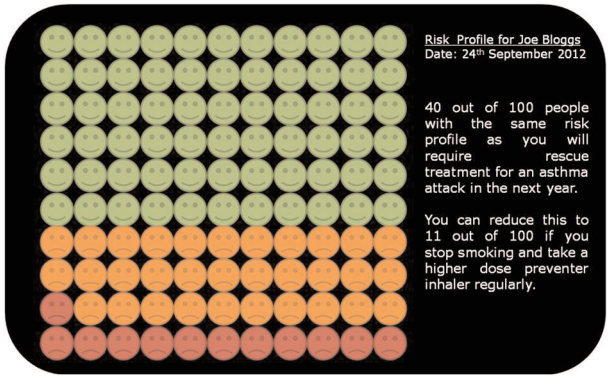
A




B

| | Treatment | |
|---|---|---|
| | Current Guideline | Proposed Scheme |
| **Patient A:** High symptom burden, low risk | Continuous oral corticosteroids<br>High dose inhaled corticosteroid<br>Long-acting beta-agonist<br>Additional drug (e.g. montelukast)<br>Short acting beta-agonist | Low dose inhaled corticosteroid<br>Long-acting beta-agonist<br>Long-acting anticholinergic<br>Short acting beta-agonist<br>Specialist services intervention (weight loss/ speech therapy/ physiotherapy/ psychology) |
| **Patient B:** High risk, few symptoms reported | Short-acting beta-agonist | Phenotype-specific anti-inflammatory: oral corticosteroids<br>Formal concordance assessment<br>High dose inhaled corticosteroid<br>Short acting beta-agonist |
| **Patient C:** Smoker with symptomatic airway damage | Continuous oral corticosteroids<br>High dose inhaled corticosteroid<br>long-acting beta-agonist<br>additional drug (e.g. montelukast)<br>Short acting beta-agonist | Phenotype-specific anti-inflammatory: macrolide<br>Formal concordance assessment<br>Long-acting anticholinergic<br>High dose inhaled corticosteroid<br>Short acting beta-agonist |

**Figure 4. Example of communication following an asthma risk assessment. This approach has the potential to improve understanding of the rationale for an asthma treatment, facilitate shared decision-making, and may improve concordance**




inhaler technique checked with all the devices they use,[112] and suggest that the responsibility for this assessment should be explicit in local guidelines.

### Shared decision-making about risk

The proposed approach has an additional advantage: by artificially separating the domains of control and risk it can become more straightforward to discuss treatment changes with patients. People with asthma can decide whether a gain in daily control is worth the potential burden of additional medications if no reduction in risk is to be expected. Similarly, by explicitly addressing risk, individuals with asthma can make informed decisions on lifestyle choices and escalation of treatment. Their current risk and the effect of an intervention can be made explicit to assist in the shared decision-making process (see example in Figure 4),[113,114] as occurs in other areas of medicine.[115] Giving information like this has the potential to influence for the better a patient's health-related choices[116] and may improve health literacy. Collaborative discussion around risk and symptoms management to aid informed decision-making is consistent with motivational interviewing, an approach shown to improve concordance in asthma.[117,118] An explicit consideration of risk may also improve the engagement of some groups with 'preventer' treatment (e.g. adolescents appreciating the risk of being unwell for examinations or sporting commitments).

## Conclusions

Asthma attacks matter to people with asthma, healthcare professionals, and budget holders. Identifying those at risk of an asthma attack is therefore important. The focus of current treatment guidelines on a universal stepwise approach driven by daily asthma control is of limited efficacy, can expose patients to unnecessary risk, and has the potential to neglect non-pharmacological interventions. In this article we argue that a more explicit separation of asthma control and risk is consistent with pathophysiological processes and will lead to more appropriate clinical decisions and treatments for both of these important related domains. We acknowledge that our understanding of the factors contributing to the risk of asthma attack is far from complete, and that our suggestion for a revision to management guidance is at an early stage. However, similar strategies have proved successful in other conditions in general practice, such as managing the risk of a future myocardial infarction rather than simply current angina symptoms. When such an approach is refined, it has the potential to begin to reduce morbidity both from asthma and from inappropriate treatments, may increase patient engagement and concordance, and could lead to considerable financial savings.

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