

# Complexity of chronic asthma and chronic obstructive pulmonary disease: implications for risk assessment, and disease progression and control

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Although assessment of asthma control is important to guide treatment, it is difficult since the temporal pattern and risk of exacerbations are often unpredictable. In this Review, we summarise the classic methods to assess control with unidimensional and multidimensional approaches. Next, we show how ideas from the science of complexity can explain the seemingly unpredictable nature of bronchial asthma and emphysema, with implications for chronic obstructive pulmonary disease. We show that fluctuation analysis, a method used in statistical physics, can be used to gain insight into asthma as a dynamic disease of the respiratory system, viewed as a set of interacting subsystems (eg, inflammatory, immunological, and mechanical). The basis of the fluctuation analysis methods is the quantification of the long-term temporal history of lung function parameters. We summarise how this analysis can be used to assess the risk of future asthma episodes, with implications for asthma severity and control both in children and adults.

## Introduction

Bronchial asthma and chronic obstructive pulmonary disease (COPD) are the two most common chronic respiratory diseases, affecting millions of children and adults. Nevertheless, many features of these diseases, including pathogenesis and progression are not fully understood. To treat patients with asthma or COPD correctly, markers of disease severity and control<sup>1</sup> are needed that can be used to predict future exacerbations.<sup>2</sup>

However, in bronchial asthma the association between stimuli and exacerbations is poor<sup>3–5</sup> and increasing evidence suggests that the classic paradigm of asthma, sequentially linking the trigger to the symptoms (figure 1), is incomplete in many situations. Indeed, the association between trigger and inflammation,<sup>6,7</sup> inflammation and bronchial hyper-reactivity,<sup>8–12</sup> and airway obstruction and symptoms is not always strong. Asthma phenotypes are very heterogeneous—eg, inflammation can be predominantly eosinophilic, neutrophilic, or involve other pathways.<sup>13–19</sup> Many inflammatory pathways that are part of the asthmatic cascade operate within a complex web of interactions, including various subsystems that are part

of the host defence, immunity, and inflammation, and lung mechanics. Although COPD is different, the distinction between it and asthma is beginning to blur.<sup>20,21</sup> Additional interactions can occur between the organism and the environment, with several external heterogeneous triggers (eg, viral infections, allergens, and pollutants), showing high temporal variability.

Assessment of asthma severity and control based on one clinical marker, such as the averaged set of symptoms, has limitations because of the complexity of the disease. A multidimensional approach with more than one parameter or including statistical measures of parameters with time should provide a more comprehensive picture of the disease process. In this Review, we will explain the unpredictable nature of clinical events and exacerbations based on the complex and non-linear behaviour of the respiratory system fluctuating with time. Specifically, we will discuss how the network structure of the airway tree and the lung tissue contributes to unexpected sudden disease exacerbations in both asthma and emphysema. With fluctuation analysis of the history of physiological parameters, we show how prediction of exacerbations and hence treatment strategies might be improved.

## Classic method of assessment of asthma control and severity

Asthma severity can be considered as the intrinsic intensity of the disease and is measured most easily and directly when a patient is not under long-term control treatment. Asthma control is the degree to which the manifestations of the disease (ie, symptoms, functional impairments, and risk of exacerbations) are minimised by treatment. Disease severity and control form the basis of asthma treatment according to the global strategy for asthma management and prevention guidelines,<sup>1,22</sup> and both include the present impairment and future risks. Assessment of the present impairment is easier and related to the frequency and intensity of symptoms, including impairment of quality of life

## Search strategy and selection criteria

The paper does not fulfil the criteria of a systematic review (Cochrane) of a single topic, but includes several specialties with references. The paper thus contains elements of a perspective with models and hypotheses. We searched Medline (National Center for Biotechnology Information) with the search terms “asthma control and lung function”, “asthma risk”, “asthma monitoring”, “disease progression and COPD”, “fractal” in combination with “lung” and “respiratory system”, “long range correlation and lung function and lung”, and “complexity and lung function”. We focused on children. We largely selected publications in the past 10 years but did not exclude commonly referenced and highly regarded older publications. We searched the reference lists of articles identified by this search strategy and selected those we judged relevant. Review articles and book chapters are cited to provide readers with more details and references than this paper has room for. Our reference list was modified on the basis of comments from peer reviewers.

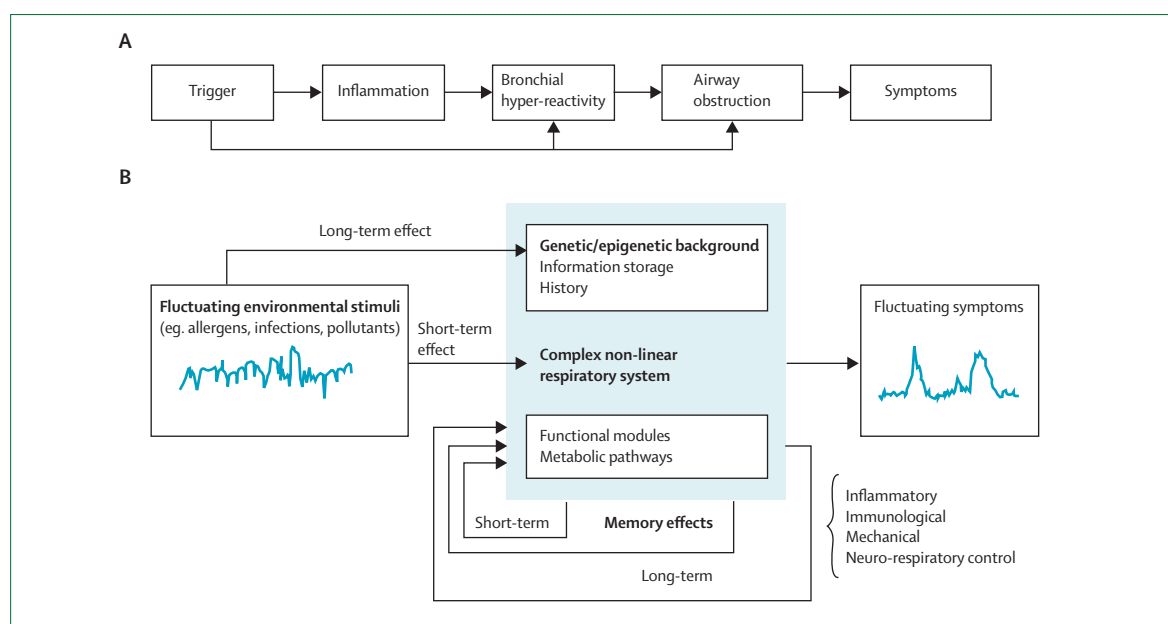


Figure 1: Reductionist (A) and complex-systems (B) approaches

(night-time awakenings, need for short-acting  $\beta_2$  agonists for quick relief of symptoms, work or school days missed, and ability to engage in normal daily activities) and functional limitation. However, evidence suggests that individual perceptions of symptoms or severe exacerbation vary among patients, and that difficulties in the perception of body sensations and expression of emotions<sup>23</sup> are more frequently associated with severe asthma and near fatal asthma. These difficulties suggest that additional objective parameters for the description of asthma severity are needed. The preferred method for objective assessment of functional limitation is to characterise lung function with spirometry, including indices such as forced expiratory volume in 1 s ( $FEV_1$ ), forced vital capacity (FVC), and the  $FEV_1/FVC$  ratio. Spirometry is widely used to define severity in adults.<sup>1</sup> Most school children have normal  $FEV_1$  values irrespective of their asthma severity as defined on the basis of symptoms.<sup>24–26</sup> In children, the  $FEV_1/FVC$  ratio seems to be better associated with asthma severity than in adults.<sup>24,25</sup> Although peak expiratory flow (PEF) is not reliable for the assessment of the severity of airway obstruction,<sup>27,28</sup> studies in adults have shown that it can be a useful method to monitor trends and quantify the history of asthma control.<sup>29</sup>

### Risk assessment and prediction of exacerbations

The risk or likelihood of asthma exacerbations is difficult to predict, and disease severity and risk of exacerbations are not always closely associated,<sup>30</sup> because some patients who have few symptoms or impairment of quality of life might still be at serious risk of severe, even life-threatening, exacerbations.<sup>31</sup>

Many studies have tried to identify clinical risk factors that predict severe airway obstruction or re-admission rates on a short-term basis.<sup>2,13,32–47</sup> Evidence suggests that frequent asthma symptoms, repeated hospital admissions or emergency visits in the past, frequent use of inhaled short-acting  $\beta_2$  agonists, present use of systemic corticosteroids, or recent withdrawal from systemic corticosteroids are risk factors for future asthma exacerbation, admission, or even death.

Very few studies have addressed the issue of lung function as a predictor of admission or asthma exacerbation in the short term. Low values of  $FEV_1$  and maximum mid-expiratory flow have been proven to predict subsequent asthma episodes in longitudinal trials in adults<sup>48</sup> and children,<sup>49–51</sup> respectively. The predictive value of bronchial hyper-reactivity for asthma relapse during stepwise reduction of inhaled corticosteroids was reported in studies.<sup>52,53</sup> Such data are consistent with the results of Sont and coworkers,<sup>54</sup> who showed improved asthma control if bronchial reactivity tests were used to guide asthma treatment. PEF monitoring reduces unscheduled doctors' visits in adults,<sup>55</sup> and PEF variation after bronchodilator response has been proven to be related to admission rates in adults and children.<sup>44,56,57</sup> However, lung function deterioration and exacerbation risks are not always closely associated in children; Fuhlbrigge and colleagues<sup>51</sup> reported that even children who had normal values of lung function had exacerbations.

The assessment of comorbidities, environmental risk factors, and many biomarkers—such as blood or sputum eosinophils, eosinophilic cationic protein, fractional exhaled nitric oxide concentration, serum immunoglobulin E, number of positive skin tests, pH, inflammatory mediators, or various metabolites in

exhaled breath condensates—have been proposed as potential markers of the asthma exacerbation risk in adults and children.<sup>58</sup> Some of these markers, such as fractional exhaled nitric oxide concentration, might contribute to a better definition of the eosinophilic asthma phenotype by contrast with viral wheezing disorders of early childhood, and could be useful for the prediction of the exacerbation risk in individual patients.<sup>4,19,52,53,59–65</sup>

The updated global strategy for asthma management and prevention guidelines<sup>1</sup> have placed the emphasis for treatment of asthma mainly on control. However, both severity and control include the present impairment and future risks. The association between severity and control is multidimensional, highly complex, and varies with

time. Assessment of a patient's asthma control alone might result in the loss of important information. We postulate that new methods that can account for the complex time-varying interaction between severity and control could provide improved insight into the disease process in the future.

### Multidimensional approaches

In practice, clinicians implicitly use a probabilistic approach<sup>66</sup> to monitor and treat their patients. Clinicians see the asthmatic lung as a complex web of interacting components, and they are used to integrating probabilistic knowledge about various clinical tests and biomarkers to make informed decisions about treatment. We believe that clinical experience is invaluable for the treatment of complex diseases with several interacting components. In clinical science, this approach has been adapted with the design of multidimensional asthma severity assessment strategies.<sup>22,67</sup> Standardised questionnaires like the asthma control test,<sup>68</sup> childhood asthma control test,<sup>69</sup> asthma control questionnaire,<sup>70</sup> asthma therapy assessment questionnaire control index,<sup>71,72</sup> global initiative for asthma,<sup>22</sup> and the national asthma education and prevention programme<sup>73</sup> have been developed to help with the assessment of disease severity and to guide control. In such tests, clinical symptoms, activity limitation, rescue medication, lung function, and self-perception of control are assessed in varying combinations. Although physicians are able to identify lung abnormality as obstructive,<sup>74</sup> clinical assessment of the degree of airflow obstruction<sup>75</sup> or prediction of whether the obstruction is reversible is difficult<sup>74,76</sup> because pulmonary function measures do not always correlate with symptoms. In a study, a third of children with moderate to severe asthma were reclassified to a more severe category when FEV<sub>1</sub> was considered in addition to symptom frequency.<sup>77</sup> Conversely, most children in another study who had mild-to-moderate asthma classified by symptoms had normal FEV<sub>1</sub>.<sup>74</sup>

Inflammatory markers, such as fractional exhaled nitric oxide concentration, have been used instead of symptoms to monitor disease control.<sup>4,52,53,59,78</sup> New multidimensional methods to characterise and monitor the complexity of asthma have been proposed for use in clinical disease; these methods include gene-expression profiles (genomics and proteomics<sup>79</sup>), volatile organic compounds,<sup>80</sup> or mixtures of metabolites in exhaled breath condensates (eg, metabolomics<sup>81</sup>). Some of these new methods use a novel probabilistic approach, and have the potential to provide a comprehensive understanding of different asthma phenotypes and disease activity that is based on fewer clinical assumptions.

Thus, the description of asthma is much more comprehensive with multidimensional approaches than with symptoms alone.<sup>82</sup> The need for these approaches is further supported by factor-analysis studies showing poor correlation between various disease markers.<sup>83,84</sup>

### Panel: What are the key messages for the clinician?

#### 1 The complex nature of the respiratory system

The fluctuating nature of environmental stimuli interacting non-linearly with the complex web of immunological, mechanical, and inflammatory components of the respiratory system is responsible for the unpredictability of asthma and chronic obstructive pulmonary disease (COPD) exacerbations. However, this complexity can be characterised with appropriate statistical analysis methods.

#### 2 Fractal airway network and asthma attacks

The airways in the lung form a three-dimensional, self-similar, fractal structure. In asthma and particularly in the remodelled lung, alterations in the structural properties of the airway network make the lung vulnerable to sudden avalanches of heterogeneous airway narrowing even in the absence of a large and apparent stimulus, which contributes to the unpredictable time course of asthma, including some fatal attacks.

#### 3 Network structure of the lung parenchyma and progression of emphysema

The structure of the parenchyma forms a complex three-dimensional elastic network. In the remodelled emphysematous lung, the wide distribution of mechanical forces within the alveolar wall network can lead to the rupture of elastic fibres, possibly launching a cascade of subsequent ruptures of neighbouring alveolar walls. Such an event represents an acute exacerbation with a sudden appearance of large emphysematous lesions on lung CT images and can occur even in the absence of an apparent stimulus. Such a process might contribute to the unpredictable but relentless deterioration of lung function in emphysema.

#### 4 How does a complex system approach the critical condition?

Imagine a snow field in the Swiss Alps. After heavy snow fall for several days, the snow slowly builds up layer by layer. The pressure due to the weight of the snow increases in a heterogeneous manner over the terrain until the system reaches a critical condition. Compared with the size of the field, a skier entering this terrain is a tiny perturbation. Yet the small weight of the skier can launch an avalanche. The snow field acts somewhat similar to a network, in which the present spatial distribution of forces is a consequence of events in the past with a cumulative effect on the present critical condition of the network. However, when the system is perturbed, the reaction occurs suddenly with substantial redistribution of forces during the cascade. The spatial progression of the cascade is similar to the catastrophic shift in an asthma attack or the sudden appearance of bulla in emphysema. The history of cascades becomes a process that is correlated during a long period, called long-range correlations. Such correlation properties contain information about the past and present conditions of the system. The knowledge of the correlations would allow us to predict future events in a probabilistic manner. To measure such long-range correlation properties, the system needs to be assessed during a long period and the correlation properties have to be extracted from the irregular fluctuations of a given output variable (see below).

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## Unpredictability of disease progression

Clinicians are well aware of the difficulties in trying to predict the temporal fluctuations in disease progression or prognosis even with multidimensional approaches. The assessment of the risk of future asthma exacerbations, progressive reduction in lung function, or risk of adverse effects from medication remains elusive, and the time course of events is often unexpected. For example, small or even undetected triggers can lead to unexpected fatal asthma attacks,<sup>3</sup> and even children with normal lung function can have exacerbations.<sup>51</sup> In patients with COPD, the frequency of acute exacerbations have been linked to a reduction in lung function with age.<sup>85–87</sup> Hence, the possibility exists that disease progression can occur in sudden acute steps, both in asthma and COPD. As a novel hypothesis of why this is the case, we propose several reasons related to the fluctuating nature of the environmental stimuli and their interaction with the complexity of the respiratory system (panel, key message 1).

## Fluctuating and heterogeneous environmental stimuli

The respiratory system is constantly exposed to different and time-varying stimuli. We often assume that the strength of the environmental stimulus is proportionally related to the resulting physiological effect in the airways and that this effect occurs instantaneously without any delay as embodied in the idea of bronchial hyper-reactivity (measured by the bronchial challenge test). However, several examples show that the effects can arise with lags and are dependent on the nature of stimulus. For example, Gent and colleagues<sup>89</sup> reported that although environmental pollution varies widely with time and that the amount of pollution is associated with time-dependent fluctuations in respiratory symptoms in patients with asthma, the fluctuations in exposure and symptoms are only weakly related. Another example is provided by Vahlhviist and co-workers,<sup>90</sup> who showed that during the birch season, the environmental allergen concentrations fluctuate with time, resulting in variations in fractional exhaled nitric oxide concentrations, lung function, and symptoms. Time lags between pollen stimuli and resulting inflammatory markers might even occur.<sup>60</sup> However, the association between stimuli and these biomarkers is weak and inconsistent.

Similarly, exposure to fine particulate matter (less than 2.5 µm in diameter) has a delayed effect on lung function, appearing only after 3–5 days, whereas exposure to the ozone has an immediate effect after 1 day.<sup>91</sup> The existence of lag effects with the sustained effect of environmental stimuli implies information storage or memory in the respiratory system and that a cumulative effect can potentially be built up. Thus previous stimuli are important since each particular stimulus in the past might add to the cumulative effect. Other clinical examples of longlasting environmental effects on the

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## 5 Long-range correlations in daily lung function parameters, and asthma severity, stability, and risk prediction

Long-term fluctuations of lung function parameters with time (months) are not random, but past and present values are inter-related such that they show weak, measurable fractal-type long-range correlations. These correlations can be fully characterised by the long-range correlation exponent  $\alpha$ , which indicates the temporal history of the disease and, hence in the future, could be a new additional descriptor of disease severity and phenotypes, and is a predictor of future obstructive exacerbations in chronic airway diseases.

## 6 Complexity and temporal effects of treatment

Regularly given short-acting bronchodilator treatment can act as a series of on and off stimuli. In the presence of the unfolding effect of disease history with long-range correlations, such a stimulus can result in an unstable non-linear system that generates increased randomness and variability with reduced predictability. Thus, the response to  $\beta_2$  agonists is related to the complex dynamic regulation of airway function in asthma. Fluctuation analysis has the potential to identify patients who might respond well or poorly to treatment with increased accuracy. Therefore, consideration of the timing effects of regularly given drugs on the system dynamics of a chronic disease might be necessary.

## 7 Complexity and risk prediction

For the risk prediction of future obstructive events, not only is the present value of peak expiratory flow is important, but also the long-range correlations embedded in many previous events and thus the history of the patient are crucial.

## 8 Asthma monitoring and risk prediction

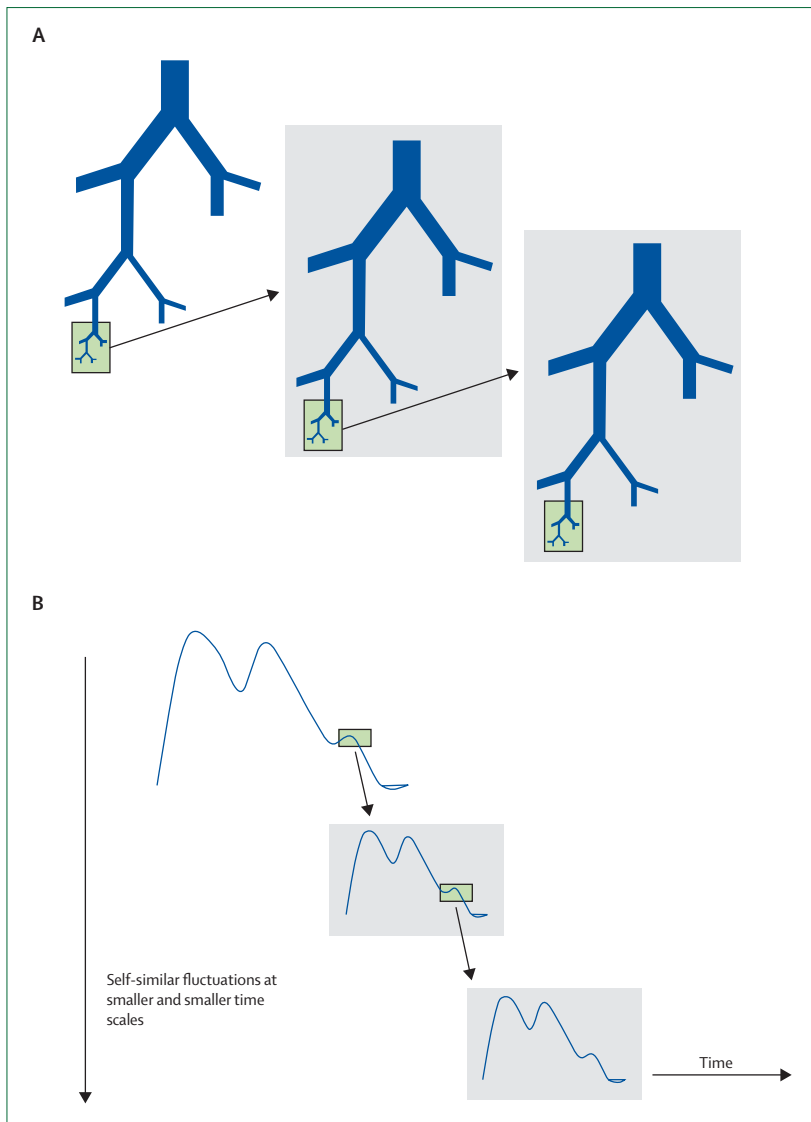
Observation of the long-term temporal fluctuation of one or even several (multidimensional) clinical and physiological markers and the analysis of their time correlation properties can add an additional dimension to better assess severity and design control of asthma or COPD in future monitoring and risk prediction concepts.

## 9 Complexity and importance of clinical experience

The physicists Goldenfeld and Kadanoff<sup>88</sup> said "As science turns to complexity, one must realize that complexity demands attitudes quite different from those heretofore common in physics". We would like to add biology and medicine to the list. The experienced general practitioners would intuitively agree with this statement since it is not only necessary to know the pathophysiological mechanisms of a disease, but the clinician's personal experience with the patient's complex behaviour observed during a long period is of equal importance. The careful and quantitative assessment of the patient's history should allow an improved prediction of the patient's disease stability.

respiratory system and its immune response might be the persistent bronchial hyper-reactivity after one allergen challenge<sup>92</sup> or the longlasting, sustained effect of drug treatment for a few weeks after cessation of treatment.<sup>93</sup> Furthermore, the temporal pattern of environmental triggers is usually not entirely random but correlated. For example, viral triggers are associated with each other and the climate,<sup>94</sup> and show seasonal temporal changes similar to those of pollen. Time correlations exist for pollutants.<sup>95</sup>

Thus, fluctuating environmental and treatment-related stimuli interact with the highly complex respiratory system, resulting in an unpredictable temporal pattern of respiratory symptoms and lung function changes (panel, key message 1).



**Figure 2: Fractal properties of structures (A) and time series (B)**

Shown is an idealised fractal structure and time series in which the fluctuations at different spatial and time scales are similar, respectively.

### Complexity of the respiratory system

Our understanding of the pathophysiology of the respiratory system has traditionally followed a reductionist approach (figure 1) whereby researchers isolated and identified specific mechanisms from the complex web of interacting subsystems. With this approach, the system is divided and studied at ever increasing resolution with the ultimate goal of reconstruction of the behaviour of the whole system. In the reductionist approach, the classic understanding of asthma is based on the notion that a trigger can induce, reactivate, or sustain airway inflammation or bronchial hyper-reactivity, leading to airway obstruction and symptoms. Despite many fundamental advances, the reductionist approach also has many important limitations because it assumes that with knowledge of the

properties of every part in isolation, the response of the entire system to any stimulus can be predicted.<sup>96</sup>

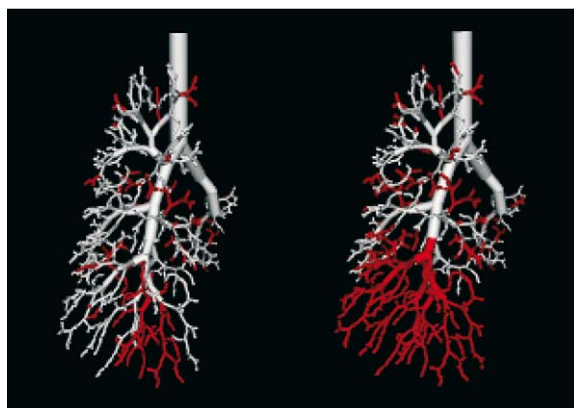
Most biological systems are complex with a hierarchy of embedded feedback loops of subsystems (eg, immunological, inflammatory, lung mechanics, and neuro-respiratory control) that function on the basis of interactions between many components and modify environmental inputs (such as allergen exposure, infection, and air pollution), leading to fluctuations in output or symptoms (figure 1). The stimulation of one component could affect a large number of other subsystems. Furthermore, the interaction between two subsystems is usually non-linear, which means that doubling input from one to the other does not result in a proportionate doubling of the response. Such non-linearities can even generate conditions in which several types of responses are possible. A range of external conditions and stimuli can interfere with the functioning of the subsystems. Furthermore, as clinical experience suggests, when the environmental stimulus is very strong (eg, severe viral infection), the response of the respiratory system will probably be dominated by the properties of the trigger. However, a series of weak irregular external environmental stimuli can trigger a specific response in a particular subsystem that might in turn propagate and potentially amplify in a non-linear cascade through other subsystems. Thus, even if all the inputs were known, which is unrealistic, the multitude of non-linear interactions and feedbacks coupled with the memory of the subsystems at different time scales hinder the accurate prediction of an output variable.

Asthma is the best example of a disorder that shows complex behaviour. Comprehension of the functioning of such systems and prediction of events such as an asthma episode are not possible within the realm of the reductionist analysis. Rather, such complexity requires new considerations and a probabilistic systems approach. Although such complex behaviour can be shown in most respiratory subsystems, we discuss two specific examples—ie, lung function in asthma and emphysema—in which correlations dependent on the fractal and network structures of the airways and parenchyma, respectively, help explain disease progression (eg, in emphysema) and have implications for risk prediction in asthma.

### Fractal airway structure: implications for sudden airway narrowing and fatal asthma

Fractals are self-similar structures in which magnification of the subparts resembles the entire structure (figure 2).<sup>97–100</sup> The three-dimensional structure of the airway and vascular trees are examples of distribution networks with fractal organisation. The self-similarity manifests in a branching pattern that repeats itself on several length scales. To describe their properties, the variations in a given structural feature should be measured at different length scales. The way these variations depend on the length scale can then be used





**Figure 3: Avalanche-like opening of the lung during slow inflation**

This behaviour can be simulated in a three-dimensional model of the airway tree before (left) and after (right) a simultaneously avalanche-like opening of many segments. White and red are closed and open segments, respectively.

to characterise the entire structure with one number, the fractal dimension. Although fractality is optimum for lung growth<sup>101</sup> and lung ventilation,<sup>100</sup> it also causes some unexpected peculiarities in diseases.<sup>98,102</sup> For example, in a lung with mild ventilation in the homogeneities, bronchoconstriction and airway reopening do not take place with equal probability in every airway. Although, the distribution of ventilation in asthma is heterogeneous,<sup>103</sup> Venegas and colleagues<sup>104,105</sup> showed with PET imaging and computer modelling that once smooth-muscle activation reaches a critical level, localised clusters of poorly ventilated lung areas can develop abruptly in discrete steps. These steps are called catastrophic shifts or avalanches, leading to new stable conditions. Because of the fractal structure of the airways with their elastic interactions through the parenchyma, small initial heterogeneities that are always present, especially in the diseased lung, can be amplified, leading to sudden self-organised patches of poorly ventilated lung regions with dispersed airway closure during bronchoconstriction. An important implication is that an airway cannot close or open without affecting the neighbouring lung parenchyma and airways. Since the airways are organised into a fractal network embedded in the elastic parenchyma, the constriction of one airway can propagate and cause an avalanche-like cascade of airway constrictions in large portions of the lung. The opposite process also has important clinical implications since it is needed to relax the asthmatic airways (figure 3).<sup>106</sup> Airways in a partly collapsed lung do not open in a smooth continuous way during inhalation, but instead they do so in discrete steps. When the pressure across airway closures reaches a threshold, airway segments suddenly open, filling large regions with air that allows regional alveolar ventilation.

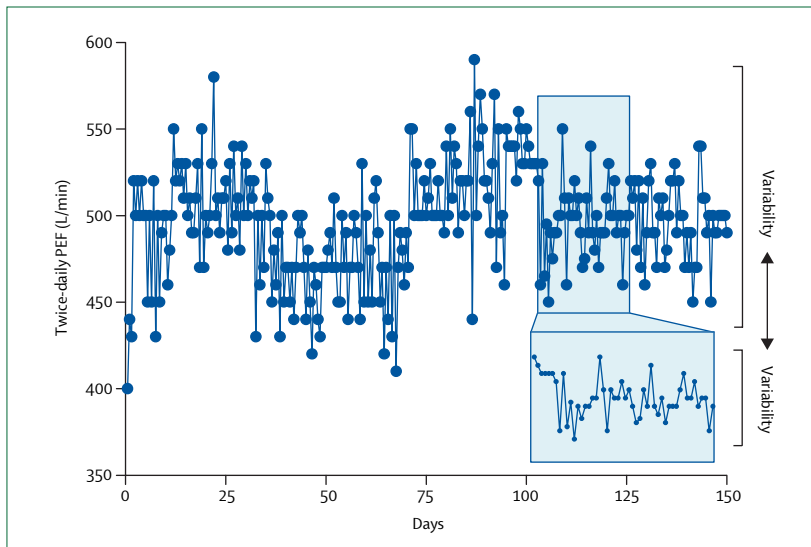
These studies provide a new way to understand the dynamics of asthma attacks. In this disease, the airways are likely to approach their local critical closing threshold pressure, which means that a small stimulus

can cause a catastrophic cascade of airway closures with severe impairment of lung function. Such threshold-based mechanisms are highly non-linear, which contributes to the poor association between the trigger and outcome in asthma. In particular, in fatal asthma the remodelled airway tree is more prone to sudden catastrophic closure and breakdown.<sup>107</sup> Thus, the history of symptom fluctuations is closely related to the structural changes of the fractal airway tree combined with the irregularities of external and internal stimuli (panel, key messages 2 and 4). Although no clinical data exist, we can speculate that the airway tree has a similar role in small airway dysfunction in COPD, given the propensity of airways in COPD to collapse during forced expiratory manoeuvres.

### **Lung tissue network structure: implications for disease progression in emphysema**

Asthma and COPD show similarities, transitions, and substantial differences.<sup>20,21,108–110</sup> One of the important differences between these two diseases is the involvement of the parenchyma. In the lung, the parenchyma forms a network of fibres, and hence network considerations might explain the progressive nature of emphysema. One feature of emphysema, an important component of COPD, results from progressive destruction of the elastic fibre network of the lung with time.<sup>110,111</sup>

High-resolution CT is a sensitive method for examination of lung structure and the changes in COPD.<sup>112</sup> Emphysematous regions of the lung (represented in CT as low attenuation areas) do not develop homogeneously, but in clusters of widely different sizes. Mishima and colleagues<sup>112</sup> showed that disease progression in emphysema is consistent with the breakdown of a network of elastic springs, and Suki and colleagues<sup>113</sup> showed that for this process to be consistent with CT images, the breakdown of the remodelled alveolar wall network has to be governed by mechanical forces. After the failure of an elastic element, stresses are redistributed in the network, and consequently neighbouring elements can become overloaded and stop functioning, which leads to failures that occur in an avalanche-like manner. Such a process leads to a wide distribution of mechanical forces in the parenchyma, predisposing an increasing number of regions to mechanical failure.<sup>114</sup> This process is perhaps the first physical mechanism proposed that can explain the progressive nature of emphysema. It is supported by CT imaging and by the fact that the condition of individuals with emphysema can irreversibly deteriorate following an exacerbation episode.<sup>115</sup> However, the question of when and where a new breakdown might arise cannot be predicted easily. Again, external triggers, such as cigarette smoke, and internal triggers, such as the subsequent inflammation-derived enzyme activity, weaken the elastic network at random locations. Thus, disease progression is not a linear sequential process but can happen in



**Figure 4: Fluctuations in twice-daily peak expiratory flow (PEF)**

Representative time series of twice-daily PEF seen during 6 months, showing self-similar fluctuations with similar variability at different time scales. The inset graph shows a shorter time scale in which the statistical properties of the PEF series are similar to those of the entire series. Despite the random-looking appearance, the fluctuations are not random but ordered, which means that any particular value is dependent on previous values.

discrete steps or as sudden deteriorations without any apparent trigger. Again, the history of exacerbations is coupled to the history of the new redistribution of structural properties in the parenchyma. Since a cascade of mechanical failures is an irreversible process that forms the microscopic basis of an acute exacerbation, at least statistically, the frequency and magnitude of such events should also correlate with deterioration in lung function.<sup>116</sup> Indeed, in clinical studies, exacerbation frequency affected the lung function and reduced the health status (panel, key message 3).<sup>85–87,117,118</sup>

### Importance of history

The above avalanche-like effect becomes relevant when forces at the microscopic scale reach a critical threshold so that a small stimulus can launch a cascade of events that propagate through macroscopically large portions of the system (panel, key message 4).

We postulate that in a chronic respiratory disease, stimuli that occurred in the past can still have an effect on the present system (figure 1). As described already, several clinical examples, such as delayed and cumulative effects of pollutants, persistent bronchial hyper-reactivity, and drug effects, show the effect of previous events (history) on the present disease state. Thus, a multitude of sustained inflammatory, immunological, or mechanical stimuli in the past can have a longlasting cumulative effect on the respiratory system in health and in disease. Although separation of individual past events might not be possible, characterisation of the history might be possible with statistical techniques. Long-range correlation analysis is an example of such a technique.

### Long-range correlation of lung function parameters

The extent of memory can be estimated from correlations within an output variable of the respiratory system. For instance, daily lung function tests or symptoms embody the features of the system's memory. Generally, the history of stimuli (or exposures) is not known, and can itself be a complex non-random process. However, when several inputs are coupled with immune reactions, inflammation, neurological control, and the mechanics of breathing, the response at the whole-organism level becomes unpredictable. Nevertheless, the overall result is that the fluctuations of the output will probably show short-term (eg, temporary airway obstruction, wheeze, and dyspnoea) and long-term (eg, persistent airway obstruction, inflammation, and permanent remodelling) correlations. Even in the unrealistic case, when all the inputs are known and experiments are done under the most carefully controlled conditions, repeated experiments would still show variability due to, for example, the microscopic instabilities in the system related to non-linearities. To characterise these fluctuations, use of statistical methods<sup>106,119,120</sup> that have been described for heart rate,<sup>121,122</sup> flow rates in river networks, and information flow in the internet is necessary.<sup>123</sup> In complex systems with an underlying fractal structure,<sup>123</sup> the fluctuations show correlations during long periods. These long-range correlations typically show self-similar statistical properties with several orders of time scales (figure 2) similar to the spatial self-similarity of fractals. Correlations can be important in risk prediction.

The usefulness of day-to-day PEF variability in the diagnosis, risk prediction, and monitoring of asthma has been discussed extensively in published work and guidelines.<sup>22</sup> We examined the day-to-day lung function fluctuations in chronic asthma.<sup>124</sup> Individual PEF values are highly variable but not random with time (figure 4). We investigated the temporal pattern of PEF in 80 individuals with asthma who had taken part in a long-term clinical trial.<sup>124,125</sup> In particular, we examined whether the statistical and autocorrelation properties of the time series of PEF recordings could be used to predict the risk of a future asthma episode. The fluctuations in the twice-daily PEF measurements assessed during 6 months showed fractal-type long-range correlations. Measures of variability and correlation properties of a signal can be analysed by various methods.<sup>126</sup> Here we discuss the detrended fluctuation analysis,<sup>120,127</sup> which is particularly suited for quantification of the correlation of the lung function history. In this analysis, the cumulative effect of how fluctuations in the past affect fluctuations in the present as a function of the time scale  $\tau$  or how far the fluctuations occurred in the past is quantified by the fluctuation function  $F$ . Often  $F$  follows a power function—ie, it is roughly proportional to  $\tau^\alpha$ , which characterises the complex self-similar behaviour with the long-range correlation exponent  $\alpha$ . This number is similar to the fractal dimension

for spatial correlations.<sup>128–131</sup> A value of 0.5 for  $\alpha$  represents a random process in which one fluctuation does not affect the next. A higher value of  $\alpha$  means greater correlation with the time series, stronger deterministic characteristics, and longlasting effects (figure 4). Importantly, evidence suggests that  $\alpha$  in the PEF series ranges between 0.6 and 0.9. Low  $\alpha$  is associated with increased asthma severity.<sup>124</sup>

In a temporal process, displaying long-range correlations, the magnitude of fluctuations that occurred in the past is correlated to the present and future values. Typical of fractal processes, the effect of previous fluctuations decreases slowly (according to a power law) as we look further in the past. The value of  $\alpha$ , and hence the strength of these long-range correlations, will be affected by the integrated contribution of many processes, including both external stimuli and internal mechanisms (eg, inflammatory, immunological, remodelling, and mechanical). Thus, asthma being a chronic disease shows a complex behaviour, resulting from internal memory,<sup>124</sup> and therefore requires a systems approach.

#### Long-range correlations, functional asthma phenotype, and disease stability

Long-range correlations can provide information about the stability of a complex system. A high value of  $\alpha$  (ie, more deterministic) is consistent with a functionally more stable system, whereas a low value (ie, more random) is consistent with a more unstable and unpredictable lung function. However, the mean value of the fluctuating parameter should be taken into account. Theoretically, a high mean PEF value combined with a high  $\alpha$  represents a stable healthy system, whereas a low mean PEF combined with a high  $\alpha$  value might be perceived as an airway disease with remodelled airway structure but on a stable regimen and hence with good predictability. Unfortunately, there are no studies (eg, in COPD) to substantiate this scenario (panel, key message 5).

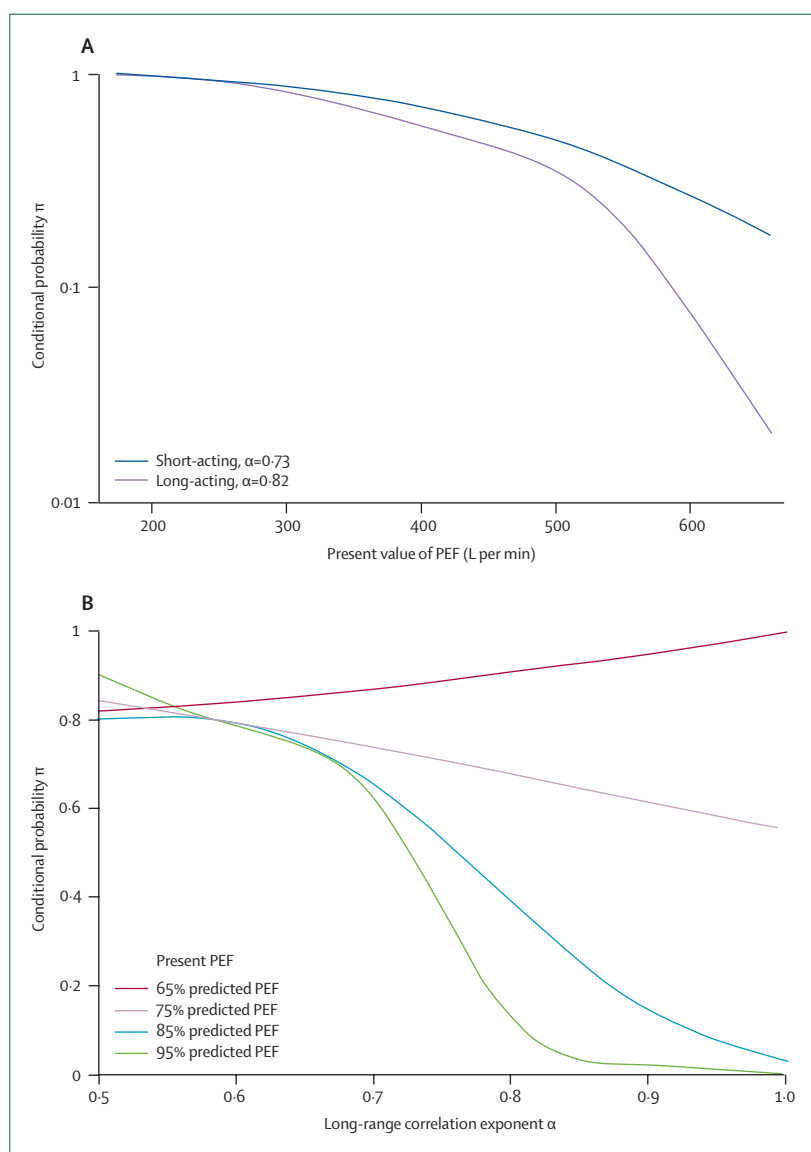
#### Long-range correlations and bronchodilator responses

We have tested the effect of treatment on disease dynamics as measured by  $\alpha$  with detrended fluctuation analysis.<sup>124</sup> Clinical and physiological data from the trial were obtained during three 6-month crossover treatments with regular short-acting  $\beta_2$  agonist given four times a day, regular long-acting  $\beta_2$  agonist, and matching placebo. During all three study periods, all patients with mild to moderate allergic asthma were on medium doses of inhaled corticosteroids. The presence and extent of long-range correlations were not affected by the long-acting  $\beta_2$  agonists. However, compared with placebo, the short-acting  $\beta_2$  agonists significantly changed the nature of correlations in the PEF time series such that the series approached a random process. Since a random process is less predictable, this finding has important consequences for the risk prediction of future severe obstructive episodes. Short-acting  $\beta_2$  agonists are the first-line drug for on-demand relief of bronchial obstruction but when given

regularly (with an inevitably long interval at night) they drive the internal regulation of airway tone towards a random process, making the system less stable.<sup>124</sup>

#### Quantification of the risk from PEF fluctuations

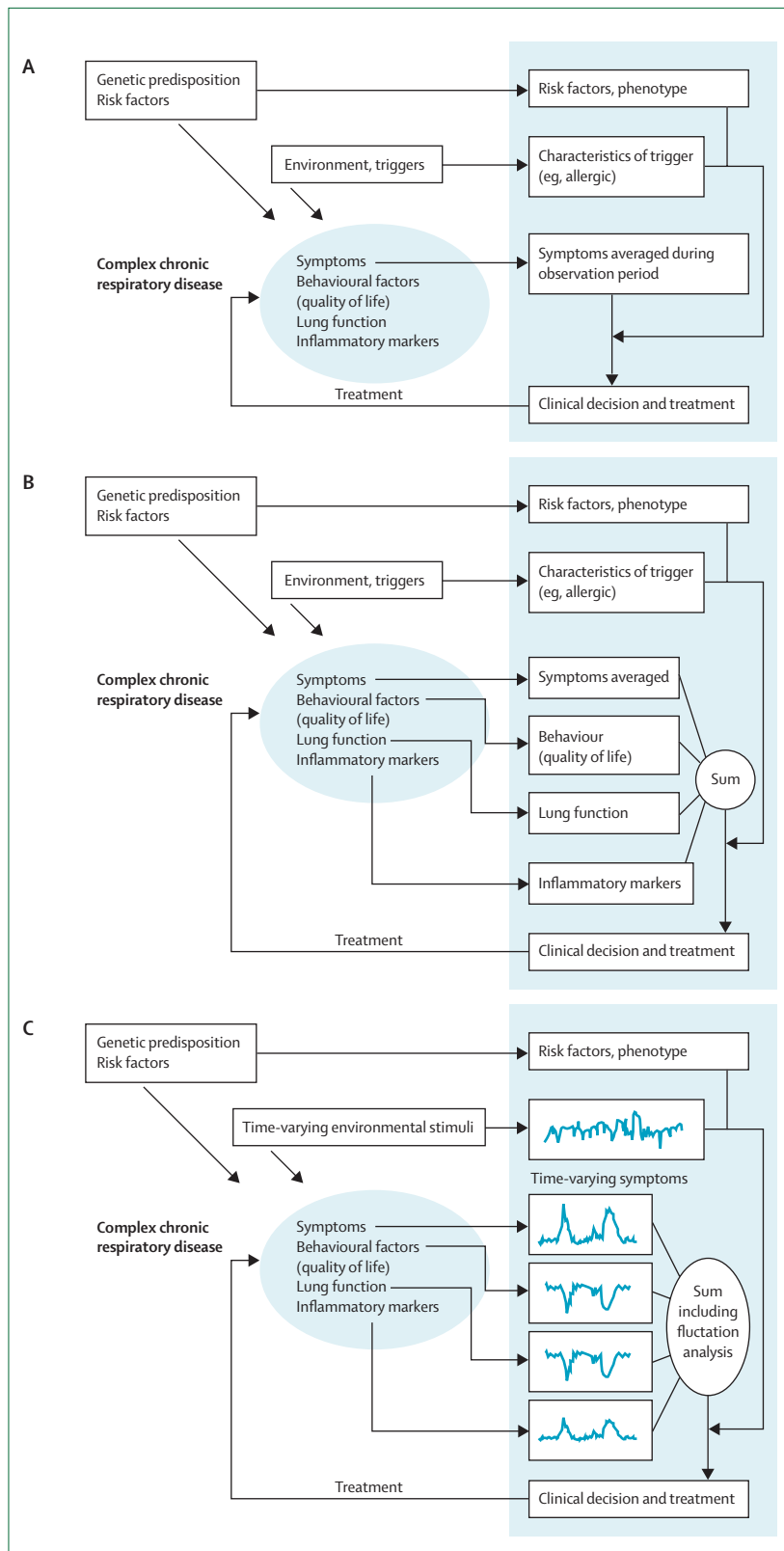
In addition to the long-range correlations, the risk of future exacerbations can be calculated from fluctuations in PEF. The conditional probability  $\pi$  that a patient will encounter a future obstructive episode (eg, with a



**Figure 5: Quantification of risk prediction of future obstructive events**

(A) Results calculated with the method proposed by Frey and colleagues<sup>124</sup> for both short-acting and long-acting bronchodilator treatments. The mean values of the long-range correlation exponent  $\alpha$  for the two groups are provided. (B) Computer simulations based on the model proposed by Frey and colleagues<sup>124</sup> show how the conditional probability  $\pi$  varies with the long-range correlation exponent  $\alpha$ . The different curves correspond to different values of peak expiratory flow (PEF). For example, the 95% predicted PEF curve is obtained by assuming that the present PEF is 95% of its predicted value, and the probability  $\pi$  that PEF is less than 80% of the predicted PEF in the next 14 days is computed for a range of  $\alpha$  values. The curves show that the risk of future obstructive events with low PEF is very dependent on  $\alpha$ .





**Figure 6: Models of classic and possible future ideas for monitoring exacerbations**  
(A) Classic monitoring method. (B) Multidimensional approach. (C) Fluctuation analysis approach.

predicted PEF less than 80%) is not only a function of today's PEF value but also depends on the long-range correlations of the time series of past PEF values.<sup>124</sup> The risk  $\pi$  is therefore not a traditional risk factor based on population statistics (eg, smoking), and represents the individual risk, varies with time, and is dependent on the history of previous events (PEFs).

Figure 5 shows how  $\pi$  varies with the present PEF during regular treatment with short-acting and long-acting bronchodilators. If, for example, PEF is 420 L per min, then the chance that PEF falls below 80% of its mean within 7 days is 68% and 53% during short-acting and long-acting  $\beta_2$ -agonist treatments, respectively. The 15% improvement results from the stronger correlations as characterised by increased  $\alpha$  during the long-acting bronchodilator treatment. Thus, by contrast with long-acting  $\beta_2$  agonists that reduce this risk, regular short-acting salbutamol increases the risk of future exacerbations (panel, key message 6).

Furthermore, with model simulations based on previous work,<sup>124</sup> we calculated how  $\pi$  depends on  $\alpha$  for several initial values of PEF (figure 5). Both the present PEF value and  $\alpha$  are crucial for estimation of the risk of future obstructive episodes. This result shows that the association between  $\pi$  and  $\alpha$  dramatically depends on the initial present value of PEF. Indeed, despite a high present PEF, a patient can have a ten-fold increased risk of a future obstructive event if  $\alpha$  is low. Thus,  $\pi$  and  $\alpha$  together might provide new measures to characterise various asthma phenotypes, describe severity, and predict exacerbations (panel, key message 7).

### Implications for the future

In complex diseases such as asthma or COPD, the description of disease severity, progression, and risk assessment is restricted with the unidimensional approach (figure 6). One possible way to address the complexity of the disease is with a multidimensional approach that includes a combination of several clinical and physiological parameters (figure 6). We have argued that observation of the long-term temporal fluctuations of clinical and physiological markers and the analysis of their correlation properties can add an additional dimension to improve the assessment of asthma severity, risk, and control, and might be used to design future drug trials. Although fluctuation analysis has been used to identify critical events in other specialties of medicine,<sup>132–134</sup> the published work on complex-system analysis in chronic asthma is still sparse. Future studies are needed to prospectively examine whether fluctuation analysis in comparison with averaged scores of symptoms is better correlated with future asthma control and exacerbation risk. Of particular interest is whether fluctuations in symptoms are related to fluctuations in lung function or inflammatory parameters and to what extent fluctuations in environmental stimuli or genetic factors affect both.

We suggest that future multidimensional approaches could even be improved by inclusion of fluctuation analysis of several parameters (figure 6; panel, key message 8). We further speculate that the complex-systems approach described here could be applicable to many other chronic diseases with long-range fluctuations in functional parameters. Clinical experience might be seen as the day-to-day way for the clinician to intuitively deal with complexity in asthma, particularly when considering the temporal history of the disease process, which can be complemented by the proposed quantitative complex system approach (panel, key message 9).

#### Conflict of interest statement

We declare that we have no conflict of interest.

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