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EDITORIAL

Identifying asthma in population studies: from single entity to a multi-component approach

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Considerable energy has been expended over the last two decades [1, 2] in developing methods for identifying the presence of asthma among participants in population studies. The objective of this endeavour has commonly been to enable epidemiological research on risk factors for asthma, with the ultimate aim of preventing the disease. However, there are other reasons for measuring the prevalence of asthma in populations, including the desire to assess the burden of disease attributable to asthma, to track changes over time, and to compare the prevalence among population groups defined by geographical, demographic or social factors. Two major international collaborative studies arising from this work have made major contributions to our knowledge about asthma [3, 4].

In this issue of the *European Respiratory Journal*, PEKKANEN *et al*. [5] have highlighted some of the difficulties that are inherent in the task of identifying asthma in population studies, and there are many. Asthma is a complex, chronic disease that waxes and wanes over cycles varying from minutes to years. This variability is a key feature of asthma. The meaning of longer-term variability in the manifestations of asthma is little understood. For example, it is not clear whether these changes reflect variation in exposure to the environmental triggers for the disease or a more fundamental, constitutionally determined time course. It is likely that both play a role. Some longitudinal patterns in childhood have been identified. The wheezing illness that is present during the first 3 yrs of life, but which disappears by the age of 6 yrs, apparently has a different aetiology to the wheezing illness that is present in school-aged children [6, 7]. Persistent and intermittent patterns of asthma are also recognised, both in adults and in children. During adult life, pregnancy and occupational exposures both contribute to changes, over time, in the manifestations of asthma. However, the causes of late-onset asthma are poorly understood. The importance of this time dimension, which is also evident in cohort studies of asthma [8–11], highlights the limitation of cross-sectional assessments of the presence of asthma for aetiological research.

There are no clinical criteria that are both necessary and sufficient for the diagnosis of asthma [12]. Many of the symptoms and signs that are characteristic of asthma, such as wheeze, chest tightness, shortness of breath and cough, are also features of other diseases, including, at various ages, chronic obstructive pulmonary disease, heart failure, gastro-oesophageal reflux, bronchiolitis and nonspecific virus-induced wheeze. Some of the symptoms, such as reports of breathlessness, also occur in people without any clearly defined illness state. People with asthma who regularly use inhaled corticosteroids may have their disease controlled to the point where symptoms (and signs) are virtually abolished for prolonged periods of time [13], adding to the difficulty in confirming the diagnosis of asthma in such people.

Physiological and pathological abnormalities are more characteristic of asthma, but these too present problems in clinical and epidemiological settings. These measures, particularly the physiological indices such as increase in lung function in response to bronchodilator, peak expiratory flow rate variability and degree of nonspecific airway hyperresponsiveness, exist in a continuum with no biologically sensible diagnostic dichotomy. Certain characteristic pathological abnormalities of the airway mucosa have been identified [14], and some of these, such as sputum eosinophilia [15] and elevated expired nitric oxide [16, 17], have been exploited for diagnostic purposes. However, the recent identification of a noneosinophilic form of asthma emphasises the potential fallibility of pathological diagnosis [18]. Of course, pathological diagnosis is not available in most clinical settings and certainly not in the epidemiological arena.

In epidemiological studies, a reported diagnosis of asthma, confirmed by a doctor, is often used as the basis for identifying cases of asthma [19]. This avoids the need for making inferences based on symptoms or physiological measurements at a single point in time. However, it does not overcome the difficulties that are inherent in making a clinical diagnosis in the first place, as described previously. Furthermore, to these problems, it adds potential errors in recall of the diagnosis among survey participants and variability among health professionals in their propensity to use the label asthma [20–24].

These problems in identifying asthma presumably stem from a fundamental problem regarding asthma: it is not a unitary entity. Rather, it is a syndrome comprised of common features that arises *via* a number of alternative pathways. How then should we proceed in applying epidemiological methods in order to improve our understanding of this disease? What measurements relevant to asthma should we make and how should we evaluate them?

In order to be useful for epidemiological purposes, the measurements used to identify outcomes or disease states

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should be both reliable and valid. Reliable measures are those that give precise and consistent results in varying settings. By using reliable measurement instruments, investigators can be assured of the greatest efficiency and minimal bias attributable to variation in the measurement of asthma status between study groups or over time. Standardised, objective tests, such as measures of lung function and airway hyperresponsiveness, are potentially more reliable than subjective measures. However, considerable efforts have been made to ensure that certain questionnaires are repeatable and can be interpreted consistently across a range of cultural settings [25, 26]. The use of the multi-item scale approach advocated by PEKKANEN *et al*. [5] is an extension of that process. These authors have constructed an internally consistent and, hence, reliable scale of questions. With each additional positive response on this questionnaire scale, there is an increase in the probability that the clinical entity that is the target of the asthma questionnaire is present.

The validity of questionnaires for the identification of individuals with asthma is commonly assessed in terms of their sensitivity and specificity for asthma [27, 28]. It is immediately apparent that there is an inherent flaw in this process. If we cannot identify asthma, how can we use ''asthma'' as the criterion against which sensitivity and specificity are assessed? This is a circular problem. PEKKANEN *et al*. [5] have recognised this problem in their evaluation of alternative measures of asthma. They estimate the sensitivity and specificity (and positive predictive value) of each measure for ''ever asthma'' and for airway hyperresponsiveness (defined as a >20% fall in forced expiratory volume in one second to <1 mg methacholine), but acknowledge that this is not an assessment of validity, rather of agreement. This assists in understanding the relationship among measures, but probably does not add much to the assessment of validity. They have also evaluated measures of asthma by the strength of their association with risk factors for asthma. While this reverses the usual logic of testing the association between risk factors and diseases, where consistent results are found in relation to several risk factors, it does increase confidence in the validity of the instrument.

The assessment of validity is crucial to understanding the meaning of the measurements we make. Without knowing what the identified outcome or clinical state represents, we cannot interpret the meaning or importance of risk factors for this outcome. How can we escape the circular problem in relation to the assessment of the validity of measures of asthma? In my view, there is no perfect or complete solution, and investigators should be cautious in claiming validity for their measures of asthma. In particular, they should be cautious in using the terms sensitivity and specificity when assessing tools for identifying asthma, as they imply a degree of certainty about validation that cannot be justified. However, if investigators focus on more limited, well-defined populations and outcomes, it may be possible to escape the circularity problem.

Accepting that there is no one ''asthma'', epidemiologists investigating the causes of the disease, or tracking its prevalence over time or between population groups, should consider measuring a range of outcomes that are relevant to the syndrome that we identify as asthma, for example, symptoms of wheeze, airway hyperresponsiveness, elevated levels of expired nitric oxide, and/or specific immunoglobulin E. Where findings such as associations with risk factors or changes over time are consistent across several of these measures, we can be confident that this is broadly relevant to asthma. For example, the finding of an increase in the prevalence of asthma symptoms and airway hyperresponsiveness between 1982 and 1992 in two New South Wales (Australia) regions [29] added confidence to the conclusion that there had been a real increase in the prevalence of asthma over this period of time. Conversely, inconsistencies in the findings in relation to these various outcomes should lead to caution in generalising the findings. In the subsequent 10 yrs, there was a decline in the prevalence of asthma symptoms and asthma diagnoses, but no change in the prevalence of airway hyperresponsiveness [30]. The explanation for this divergence in findings is unclear.

Epidemiologists' faith in the existence of asthma as a well-defined clinical entity that can be measured reliably and validly in population surveys, if only we had the right tools, may have been misplaced. In moving beyond the problem of identifying a single entity known as asthma, epidemiologists can focus on the need to characterise the relationship between risk factors and various outcomes and states that are relevant to asthma, using reliable and valid measures and with the careful measurement of potentially confounding factors. This will advance our understanding of the disease, and may ultimately lead to interventions that can prevent or ameliorate the burden of asthma.

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