The use of bronchial provocation tests for identifying asthma
A review of the problems for occupational assessment and a proposal for a new direction

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Asthma is a chronic inflammatory disease of the airways characterised by reversible airway obstruction, inflammation and hyperresponsiveness of the airway.1 For people entering occupations where currently active asthma precludes entry, such as the Australian Defence Force, a correct diagnosis ensures that those who have current asthma are identified and treated, and those who do not have a fair chance of enlisting. Failure to diagnose asthma correctly in a recruit before enlistment affects both the individual, who may have to seek alternative employment, and the employer. In the US Navy and US Marine Corps it is estimated that the cost of administrative separation of a recruit after one week in boot camp is about US$4500.2

The airways of asthmatics narrow too easily and too much in response to a wide variety of stimuli including exercise.3,4 This is known as bronchial hyperresponsiveness (BHR) and it is the physiological hallmark of asthma.4,5 The presence and severity of BHR can be measured in the laboratory or field using standardised bronchial provocation tests (BPTs).6 These tests include pharmacological challenge with agents such as methacholine and histamine and physical challenges with hypertonic aerosols, exercise, and eucapnic voluntary hyperpnoea.

Because of the variety of tests now available in Australia there is a need to re-evaluate the role of BPTs in occupational screening and to emphasise the value of objective measurement, particularly to identify exercise-induced bronchoconstriction (EIB). The aims of this article are to:

- identify problems with current practice
- discuss limitations and indications for use of BPTs in occupational screening of asthma
- propose a solution in the form of an algorithm to help standardise the protocol for screening asthma for occupational entry and establish the role of BPTs in this process.

The diagnosis of asthma

In clinical practice, a diagnosis of asthma is often made only on the basis of a positive history of wheeze and/or other symptoms consistent with asthma.2 However, epidemiologists have chosen to use recent symptoms plus a positive response to histamine/methacholine to define currently active asthma.7-9 Using this definition, an Australian study found that 25.5% of 675 adults (aged 20–44 years) had current asthma.9 The same investigators also carried out skinprick tests and found a

Abstract

- People with asthma are excluded from some occupations, including service in the Australian Defence Force, and asthma can be exacerbated by some occupations, making it desirable to identify currently active asthma and assess its severity in potential entrants.
- Objective testing of asthma is by bronchial provocation test (BPT). There are two types of BPT: direct and indirect. Pharmacological agents such as histamine and methacholine act directly on smooth muscle to cause contraction and airway narrowing. Physical challenges such as hyperpnoea and hyperosmolar stimuli cause smooth muscle contraction “indirectly” via the action of mediators released from inflammatory cells in response to the physical stimulus.
- Direct BPTs, which are commonly used in assessing ADF recruits, may not identify exercise-induced asthma, but can give false-positive results.
- For more accurate assessment, we propose a new testing algorithm consisting of two parts. The first identifies individuals with currently active asthma using indirect BPT. The second identifies individuals who may have an increased propensity for developing asthma using direct BPT.
- Standardised indirect BPTs are a practical tool for identifying active asthma for occupational entry. While the direct BPT and skin testing may help potential employees decide whether to enter occupations with a high risk of inducing asthma, it may not be ethical to use these tests to exclude them. Objective testing for currently active asthma or risk of asthma would permit fair decision-making in the workplace.
strong association between atopy and current asthma (odds ratio [OR], 5.9). Further, early-onset atopy has been found to be an important risk factor for the development of respiratory symptoms and BHR in childhood.23

One of the problems with this approach to diagnosing asthma is that individuals with demonstrable EIB may not be recognised.11,12 In a study of 802 Australian schoolchildren,11 19% had significant EIB (defined as a greater than 15% fall in forced expiratory volume in one second [FEV₁]), yet 43% did not have a clinical diagnosis of asthma. Of the 36 who underwent both exercise and histamine tests, 18 had EIB of a severity consistent with a diagnosis of active asthma (mean fall in FEV₁, 24.4%), but did not have a positive response to histamine judged either by a PD₂₀ or an abnormal dose–response ratio (PD₂₀; the provocative dose that decreases the FEV₁ by 20%).

The diagnosis of asthma is also often made on the basis of a 15% increase in FEV₁ in response to a bronchodilator. However, a negative test cannot exclude a diagnosis of asthma, as many well-treated asthmatics have normal lung function and simply do not have the capacity to increase their FEV₁ any further.

**Bronchial provocation tests**

Bronchial provocation tests using histamine and methacholine are widely used. They have been shown to be safe and to give consistent results.6 They are known as “direct” provocation tests because the agonist acts directly on specific receptors on the bronchial smooth muscle, causing it to contract.4 The agents provide a good test of bronchial smooth muscle responsiveness only to the inhaled agent. The limitations and strengths of using these agents for occupational assessment are discussed below.

The “indirect” provocation tests include exercise13,14 eucapnic voluntary hyperpnoea,15,16 distilled water,17 hypertonic saline17 and mannitol.18,19 What makes these indirect challenges with osmotic stimuli different to direct challenges is that the stimulus can act on all cells and is not acting via a specific receptor. Further, osmotic stimuli have no direct contractile effect on bronchial smooth muscle; rather, they cause inflammatory cells to release mediators that cause smooth muscle contraction. These mediators include histamine, leukotrienes and prostaglandins19,20 and probably neuropeptides. Because the airway is responding to endogenously released mediators, the indirect provocation tests are thought to reflect the neural and cellular contribution to airway narrowing and therefore are an index of currently active airway inflammation.19,21,22

This has been confirmed by findings in children (aged 8–14 years) with BHR to hypertonic saline. The BHR to 4.5% saline was strongly associated with sputum eosinophils (OR, 4.36) and sputum mast cells (OR, 7.46).23 Further, van den Berge et al22 report that responsiveness to an indirect challenge reflects indices of airway inflammation better than a direct challenge with methacholine and is superior for assessing response to corticosteroids. The editorial accompanying this study concluded that “airway responsiveness to indirect stimuli may be preferred to confirm a diagnosis of asthma”.24

**Limitations and strengths**

Although several studies have shown that BHR to histamine or methacholine correlates well with asthma severity in a clinical population, BHR to these agents is not necessarily specific to a diagnosis of asthma.25,26 Further, airway hyperresponsiveness to these agents does not necessarily reflect the presence of inflammatory cells.27 Many healthy people have been shown to have BHR to histamine. The direct BPTs cannot be used for universal screening of a healthy population for military entry.25,28-30

The data of Haby et al,11 O’Donnell and Fling,12 and Holzer et al31 demonstrate that EIB can occur in the absence of a positive response to histamine or methacholine. While the EIB in the young subjects of these studies could be due to factors unrelated to either airway inflammation or bronchial smooth muscle contraction,32 the data emphasise the importance of using indirect tests that involve a wide range of inflammatory cells producing different mediators to which the smooth muscle can respond abnormally. For example, the EIB in those subjects who did not respond to histamine provocation tests could be explained by the presence of leukotrienes that play an important role in the development of EIB.33 The concentration of leukotriene required to narrow the airway is one-thousandth that of histamine,34 and leukotrienes are found in eosinophils, the hallmark inflammatory cell of asthma. While EIB can occur without significant symptoms, it is usually associated with the presence of eosinophils35,36 and responds to treatment with inhaled corticosteroids.37 Importantly, challenge with hyperpnoea with dry air38,39 and hyperpneic aerosols39,40 can identify people with EIB.

An important limitation in interpreting a direct BPT result is the arbitrary nature of the cut-off values used to identify a positive response.30,41 These values vary considerably between laboratories and make it difficult for referring physicians to reach a definite conclusion. Cockcroft suggested that current asthma can be defined by a PC₂₀ < 1 mg/mL (PC₂₀: the provocative concentration that decreases the airflow rate by 20%), which is equivalent to a PD₂₀ of 0.5 μmol.29 However, it is common for much higher values to define responsiveness in the asthma range.25,30,42 Further, it is possible that a positive histamine or methacholine test in an asymptomatic person simply reflects airflow remodelling as a result of childhood asthma.27

To determine sensitivity and specificity of methacholine and histamine tests, James and Ryan examined the results of 18 studies and concluded that there was no consistent value that separated asthmatic from non-asthmatic subjects.43 They
found that when using a cut-off of 8 μmol or 16 mg/mL (the cut-off stipulated in ADF Protocol 701) to differentiate between a normal and an abnormal response to a methacholine or histamine test, the sensitivity ranged from 22%–100% and specificity ranged from 70%–100%. However, if the cut-off point was reduced to 4 mg/mL, the sensitivity would decrease further and the specificity would increase.

By contrast, the value for a fall in FEV₁ of 15% or more to identify asthma using the physical stimuli (indirect) tests is well beyond the mean fall of 2%–6% (SD, 2.3–5.8) found in the healthy population.16,18,44–46

The confirmation that currently active inflammation consistent with asthma is truly being identified by a positive result to an indirect provocation test comes from the studies showing that those who have positive results to these tests respond to treatment with inhaled corticosteroids, and subsequently may even have negative results to the same provocation test.37,46–49 Further, the acute airway responses to these indirect stimuli are blocked by non-steroidal anti-inflammatory drugs such as nedocromil sodium50 and sodium cromoglycate51 that have no effect in non-asthmatics. Thus, the exclusion of currently active asthma by a negative response to an indirect provocation test depends on the accurate reporting by the subjects that they are not taking anti-inflammatory medication, such as inhaled corticosteroids, at the time of the test.

Those subjects with clinically recognised asthma who have negative responses to indirect provocation tests are acknowledged to have very mild disease not requiring corticosteroid therapy and not having EIB.14

The broader problem with BPTs

Currently, a range of BPTs are available in lung function laboratories in Australia. In our experience in a large public hospital where 1500 BPTs are carried out annually, there is a lack of general knowledge about what the different BPTs indicate. Many doctors responsible for ordering BPTs are unaware that a negative response to a pharmacological agent does not exclude EIB,11,12,51 and that a positive response to methacholine or histamine may not necessarily identify currently active asthma.8,27 Many are unaware that the results of challenges with agents that act indirectly relate better to indices of airway inflammation22 and predict severity of EIB.39,40

The importance of a correct diagnosis of asthma for occupational entry

In certain occupations, such as the military, having asthma precludes entry. In other occupations, where people may be exposed to agents known to trigger asthma, pre-existing asthma may contraindicate entry. In Australia, many job applicants who are required to complete a medical history questionnaire before employment will report a history of asthma.51 Yet not all of those with a history of asthma in childhood will have asthma in adulthood, while others with no childhood history will have asthma. Others may choose to withhold information about childhood asthma or current symptoms when answering a questionnaire. The limitation in this approach is exemplified by a study of recruits to the British Army. Sinclair et al found EIB in 29 of 100 potential recruits with a history suggestive of childhood asthma, but who had been symptom-free without medication for four years.44 The dilemma of reliable history versus objective testing is further highlighted in the study by Nish and Schwietz of US Air Force recruits.52 A history of asthma after age 12 precludes enlistment in the US Air Force. Nish and Schwietz studied 192 potential air force recruits who had not had asthma since the age of 12 but failed to meet the aerobic requirements during pre-enlistment training.52 The “failed recruits” were referred to an allergy–immunology clinic for assessment, and currently active asthma was diagnosed in 113 of the 192 subjects by history, physical examination, pulmonary function tests (33%), histamine (32%), or exercise provocation (35%).

These findings suggest that a medical history questionnaire alone is inadequate and an objective protocol is needed to determine whether:

- asthma is active (and, if so, how severe it is)
- there is a propensity for developing asthma
- there are risk factors for developing asthma.

If an objective protocol for assessing asthma is used then decisions regarding employment will be made fairly. This will enable job applicants to make informed decisions before entering occupations in which work exposures may increase the risk of getting asthma or exacerbate pre-existing asthma. (Although environmental controls and safe systems of work should be in place to eliminate occupational exposures, in reality this may not be the case and workers may still be at risk.)

The problem with current protocols for asthma screening for military entry

In Australia, applicants to the ADF who have had a history of asthma within three years of their application are not permitted to enlist (ADF Protocol 701). General recruits who have had a history of asthma more than three years ago, but not in the past three years, may enlist without necessarily undergoing further objective assessment. This approach would appear to have worked well in the past, as only 40 of 1807 consultations of ADF personnel revealed asthma.53 The studies of Nish and Schwietz52 and Sinclair et al44 in recruits, and of Anderson54 in divers with no history of asthma in the last three years, demonstrate that this approach may fail to identify currently active asthma in a significant proportion of subjects. In the Australian study by Anderson of 180 potential scuba divers who had passed a stringent medical examination and had had no significant symptoms for five years, 16.6%
had a positive response to hypertonic saline (fall in FEV₁ >15%). This suggests that asthma was still active in these symptom-free subjects, who would all be considered at increased risk of bronchoconstriction from exercise or accidental aspiration while diving. Those responsive to hypertonic saline are likely to have active airway inflammation, which can be reduced by treatment with inhaled corticosteroids.

In contrast to general recruits, potential aircrew, divers, and submariners who have a history of asthma or wheeze (and who have been asymptomatic without medication for at least three years) are subject to further assessment. This assessment may include a physician examination, spirometry, and bronchial provocation testing at the discretion of the examining physician. The selection of a BPT depends on the choice made by the examining physician and the availability of tests in the laboratory to which the subject is referred. Currently a positive response to one of these provocation tests would be the basis for exclusion from these specialist occupations within the ADF. Apparently, equal weighting is given to a positive response to a direct provocation test, such as histamine or methacholine, and to an indirect provocation test, such as hypertonic saline. The US Army (AR40-501) specifies similar criteria for rejection on the basis of a positive test, such as hypertonic saline. The US Army (AR40-501) specifies similar criteria for rejection on the basis of a positive methacholine or exercise test. However, the information specifies similar criteria for rejection on the basis of a positive methacholine or exercise test. However, the information

What is not clear in the regulations is whether a negative response to inhaled histamine or methacholine permits entry into the defence forces. Considering the studies showing histamine-negative/exercise-positive results in schoolchildren, and methacholine-negative/exercise-positive results in elite athletes and defence force recruits, it may be appropriate to revise the guidelines for provocation tests to ensure that the tests used do exclude currently active asthma or EIB.

A procedure currently used by the NSW Police Service (NSW Police Medical Service, personal communication) to assess recruits would appear to be both fair and appropriate. If an applicant declares a history or symptoms suggestive of asthma he or she is advised to have a hypertonic (4.5%) saline challenge and a clinical assessment and report from a respiratory physician of their choice. If the test result is positive, the applicant is advised to consult a respiratory physician again and obtain treatment with inhaled corticosteroids and repeat the hypertonic saline challenge after a reasonable period (three months is suggested). If the response to hypertonic saline is no longer abnormal the applicant is cleared. If the initial saline test is negative, but the clinical report has significant inconsistencies, the applicant is requested to have a eucapnic voluntary hyperpnoea challenge to exclude EIB. The strength of this policy is that it recognises that, for many asthmatics, the disease is not persistent and can be controlled in a relatively short period.

**Indications for indirect BPT**

We propose that the indication for use of an indirect BPT is to identify an individual with currently active asthma. We agree with the American Thoracic Guidelines that a diagnosis of EIB “cannot be made with a methacholine test”, and that exercise is indicated “when the presence of EIB would impair the ability of a person with a history suggesting asthma to perform demanding and lifesaving work (eg, military, police, firefighters)” We suggest that surrogate challenge by other indirect stimuli, such as hypertonic saline, mannitol or eucapnic voluntary hyperpnoea, could be successfully used to identify those with EIB.

We propose that using direct challenge with a pharmacological agent to exclude currently active asthma could be inappropriate, because the cut-off value of PD₂₀ >1 mg/mL or 0.5 μmol for unequivocal asthma is low, and the higher values that are likely to be documented in a person with a past history overlap with values for normal subjects. However, for people entering an occupation where the environment has known risks for developing asthma, such as in the timber industry or occupations involving exposure to low molecular weight compounds such as isocyanates, then a positive methacholine or histamine test on entry may indicate a greater propensity for developing the disease.

**A proposed algorithm for an objective assessment of asthma**

Box 1 presents an algorithm for assessing asthma in the context of assessing a job applicant. The algorithm incorporates the use of both indirect and direct BPTs. The desired outcome of using this algorithm is to correctly identify:

- those who have and require treatment for currently active asthma
- those who do not have currently active asthma, although they have a history
- those who have a propensity for developing asthma again or for the first time (eg, those with positive BHR and positive skin tests)
- those who have no BHR and are not likely to get asthma.

**Discussion**

ADF Protocol 701 (for the assessment of asthma for general enlistment) relies on subjective reports of history of asthma via medical history questionnaires. The need for objective measurement is exemplified by the studies of Nish and Schwiete, Sinclair et al and Anderson et al, which clearly demonstrated that questionnaire data are unreliable and that, even when used in conjunction with a medical examination, diagnosis of active asthma can be missed. Applicants to the
I: Algorithm to assess asthma in potential ADF recruits

To diagnose currently active asthma for occupational entry

Measure spirometry (FEV₁, FEV₁/FVC, FEF₂₅₋₇₅)

? Normal (see Box 2) No

? Mild obstruction* No

Administer bronchodilator

Disp. bronchodilator

Do indirect BPT

? Lability (>23%) Yes

Currently active asthma unlikely

? Positive Yes

Currently active asthma

? Reversibility (>15%) Yes

Severe chronic asthma or other disease

? Reversibility (>15%) Yes

Severe chronic asthma or other disease

Interpretation of spirometry (modified from Gold):

<table>
<thead>
<tr>
<th>FVC*</th>
<th>FEV₁</th>
<th>FEV₁/FVC†</th>
<th>FEF₂₅₋₇₅†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>&gt;80</td>
<td>&gt;80</td>
<td>&gt;70</td>
</tr>
<tr>
<td>Mild obstruction</td>
<td>66-80</td>
<td>66-80</td>
<td>60-70</td>
</tr>
<tr>
<td>Marked obstruction</td>
<td>&lt;66</td>
<td>&lt;66</td>
<td>&lt;60</td>
</tr>
</tbody>
</table>

*Per cent of predicted normal; †Absolute value; ‡Many athletic people have a low FEV₁/FVC ratio because their FVC is higher than average. This should be considered when interpreting spirometry in military recruits.

Criteria for a positive test depend on which BPT is performed

Indirect
- Exercise: fall in FEV₁ of 10% or more from baseline
- Hypertonic saline: fall in FEV₁ of 15% or more from baseline
- Eucapnic voluntary hyperpnoea: fall in FEV₁ of 10% or more from baseline
- Mannitol: fall in FEV₁ of 15% or more from baseline

Direct
- Methacholine and histamine: PD₂₀ < 3.9 µmol or 7.8 mg/ml

Lability
A lability above 23% would indicate currently active asthma. The calculation is:

\[
\text{Lability} = \frac{\text{highest FEV₁ after bronchodilator} - \text{lowest FEV₁ after provocation test}}{\text{baseline FEV₁}} \times 100\%
\]

Skin prick tests
A positive skin prick test is defined as a wheal of 2 mm or more after 15 minutes.

Atopy
Atopy only increases the risk of developing asthma for some occupations, but it is a risk factor for asthma independent of occupation.

Diagram 1

Diagram 2

To determine the propensity for asthma to develop

Perform skin prick tests

Do direct BPT

Low propensity for asthma to develop, lower if non-atopic No

? Positive Yes

Propensity for asthma to develop; higher if atopic

Reversibility
An increase in FEV₁ of 15% or more after administering bronchodilator is significant and may be consistent with currently active asthma.

A positive skin prick test is defined as a wheal of 2 mm or more after 15 minutes.

Atopy
Atopy only increases the risk of developing asthma for some occupations, but it is a risk factor for asthma independent of occupation.
submarine, diving or aircraft units of the ADF who have had a history of asthma three or more years before their application are required to undergo mandatory bronchial provocation testing (ADF Protocol 701). The studies of random populations cited above (particularly the one by Pattemore et al showing that 53% of those diagnosed with asthma did not demonstrate responsiveness to histamine)28 confirm the inadequacy of histamine or methacholine testing alone for the identification of people with currently active asthma.26,28,29

To overcome the problems addressed above, one of our aims was to develop an algorithm as a step towards standardising the occupational screening protocol for asthma.

Diagram 1 of the algorithm is potentially a useful tool to identify people with currently active asthma and improve the uniformity of assessing asthma for occupational screening, in particular for the Defence Forces. This approach is likely to be acceptable and it will be clinically useful, subject to validation and the fairness of the algorithm to prospective employers. An important question arising from this algorithm is whether a subject without symptoms, but who shows significant improvement (>15%) in FEV1 following bronchodilator or who tests positive to an indirect provocation test, should be excluded from the ADF. This would not currently be the case for an applicant to the NSW Police, who would be given the opportunity of a repeat test after three months’ treatment.

One of the main reasons why questionnaire data are unreliable is because they often only represent the individual’s perception. In asthmatic subjects, there is wide variability in perception of symptoms and they do not correlate well with objective measurement.61 Moreover, the correlation is worst among those with worse asthma.62

If doctors relied solely on their patients’ perception of symptoms of asthma, then over- or under-diagnosis and treatment of the disease would be likely.64 However, if a subject had a positive indirect BPT, there would be grounds for exclusion from the ADF on the basis of underlying inflammation in the airway consistent with currently active asthma, regardless of the presence or absence of symptoms.

The purpose of Diagram 2 in the algorithm is to provide information to job applicants who may have a propensity to develop asthma and who may be considering entering an occupation where the possibility of workplace exposure could put them at risk of developing asthma. This information would enable candidates to make informed decisions about whether they should enter an occupation associated with known risks for the development of asthma. However, this element of the algorithm may be contentious, in that there should be no occupation where work exposure may increase the risk of getting asthma.

For those entering “at risk” occupations who do not have currently active asthma according to the protocol laid out in Diagram 1, but who subsequently test positive to histamine or methacholine, the question of whether to advise them of a potential increased risk of developing asthma is a difficult one. Although the certainty of the risk has yet to be proven and is probably different for each substance, if people are not informed it may be too late by the time a problem occurs.65 Even after the cessation of exposure, studies have shown that people with occupational asthma continue to have symptoms.66

However, identifying people with a propensity to develop asthma from pre-employment screening may also have undesirable consequences. Cases of discrimination could arise from employers denying employment to such people. Further, if they are employed and subsequently develop a problem, insurance companies may refuse to pay compensation.

While it seems logical that those with BHR may have a greater predisposition to the development of occupational asthma, this has not been confirmed in epidemiological studies. Therefore, until further research is carried out looking at the long-term changes in BHR over a cross-section of occupations, it may be difficult to justify the enforcement of a pre-employment universal screening program. However, it is probable that, in some populations, exposure–response relationships will be difficult to observe due to the “healthy-worker” effect (ie, the onset of respiratory symptoms results in

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### 2: Calculating normal ranges for spirometry — summary equations for caucasian adults aged 18–70 years*

The lower 5 or upper 95 percentiles are obtained by subtracting or adding the figure for residual standard deviation* in the last column from the predicted mean

<table>
<thead>
<tr>
<th>Variable</th>
<th>Gender</th>
<th>Unit</th>
<th>Regression equation †</th>
<th>RSD</th>
<th>1.64 RSD</th>
</tr>
</thead>
<tbody>
<tr>
<td>FVC</td>
<td>F</td>
<td>L</td>
<td>4.43H – 0.026A – 2.89</td>
<td>0.43</td>
<td>0.71</td>
</tr>
<tr>
<td>FEV₁</td>
<td>F</td>
<td>L</td>
<td>3.95H – 0.025A – 2.60</td>
<td>0.38</td>
<td>0.62</td>
</tr>
<tr>
<td>FEV₁/FVC</td>
<td>F</td>
<td>%</td>
<td>–0.19A + 89.10</td>
<td>6.51</td>
<td>10.7</td>
</tr>
<tr>
<td>FEF₂₅–₇₅</td>
<td>F</td>
<td>Lₘ⁻¹</td>
<td>1.25H – 0.034A + 2.92</td>
<td>0.85</td>
<td>1.40</td>
</tr>
<tr>
<td>FVC</td>
<td>M</td>
<td>L</td>
<td>5.76H – 0.026A – 4.34</td>
<td>0.61</td>
<td>1.00</td>
</tr>
<tr>
<td>FEV₁</td>
<td>M</td>
<td>L</td>
<td>4.30H – 0.029A – 2.49</td>
<td>0.51</td>
<td>0.84</td>
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<tr>
<td>FEV₁/FVC</td>
<td>M</td>
<td>%</td>
<td>–0.18A + 87.21</td>
<td>7.17</td>
<td>11.8</td>
</tr>
<tr>
<td>FEF₂₅–₇₅</td>
<td>M</td>
<td>Lₘ⁻¹</td>
<td>1.94H – 0.043A + 2.70</td>
<td>1.04</td>
<td>1.71</td>
</tr>
</tbody>
</table>

FVC = forced vital capacity; FEV₁ = forced expiratory volume in one second; FEF₂₅–₇₅ = forced expiratory flow through the middle portion of the vital capacity; H = standing height (m); A = age (years); L = litres

† The residual standard deviation (RSD) describes the spread of individual values about a multiple regression equation.

‡ Between 18 and 25 years, use value of 25 years in the equations, as this is valid over this range.

* Taken from Quanjer et al.63

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affected people leaving that employer permanently and entering a different field of work).66

Another issue arising from Diagram 2 relates to the inclusion of skinprick testing for the assessment of atopy for military and/or other occupations. Not all occupational asthma is related to allergy. While it is known that atopy is only a risk factor for the development of asthma in some occupations (eg, animal handling),57 atopy in general is a risk factor for asthma to develop, independent of specific work-related exposures.10 Therefore, the inclusion of skinprick testing may provide additional information to determine the propensity for an individual to develop asthma.

Sensitivity and specificity data on BPTs in screening for asthma have not been presented in this article. While the diagnosis of some diseases or conditions is confirmed or excluded conclusively by a single test, the diagnosis of asthma is often less certain. There is no “gold standard” for the diagnosis of asthma. In one study comparing physicians’ assessment of asthma and methacholine responsiveness, the physicians disagreed with the BPT result for 39% of patients.58

**Conclusion**

Using symptoms and BHR for diagnosis, the prevalence of asthma at any one time in the Australian adult population is 10%–15%. However, asthma is a disease that, in the same person, will vary in severity spontaneously over time and in response to treatment. Many factors can affect BHR (recent exposure to allergens is a good example). There is also great variation in disease severity between subjects. Most young people diagnosed at one time or another have good lung function14,50,72 and suffer attacks only from time to time or after exercise. All but a few will have evidence of allergy by skin testing. It seems unfair that these people are often viewed as the same as those who have persistent asthma and significant morbidity from their disease.

The variability of asthma makes screening with a single test difficult. The proposal here is to identify people with active asthma by using stimuli that act indirectly and involve many bronchoconstricting mediators. Thus, failure of the subject to be responsive to one mediator at the time of testing is not crucial, as it is when only a single agonist, such as methacholine or histamine, is used to provoke airway narrowing.

The measurement criteria used to identify an asthmatic can often depend on a single value, such as an abnormal response to a bronchodilator (eg, >15% baseline), so care is needed in establishing cut-off points for abnormality. The cut-off points for the responses to the indirect challenge tests used in the algorithm have been selected to be outside the 95% confidence intervals of the falls in $\text{FEV}_1$ measured in healthy non-asthmatic subjects performing the respective challenge. Those who have a response outside this range (usually defined as a greater than 10% or 15% fall in $\text{FEV}_1$) invariably become less responsive to challenge after immediate treatment with sodium cromoglycate or nedocromil sodium or long-term treatment with inhaled corticosteroids. As this reduction in airway responsiveness reflects changes in mediator release and airway inflammatory cell number, few would argue that they are not consistent with a diagnosis of asthma. For this reason, a positive response to an indirect challenge in a person not clinically recognised as having asthma is not interpreted as false, but rather as one that identifies a person who would benefit from treatment. As a corollary to this, a negative response (providing the test is carried out properly) will be obtained only when the concentrations of inflammatory cells and their mediators are insufficient to cause the airways to narrow.

People known to have mild asthma do not always have a positive response to indirect tests of BHR, and these might be called “false negatives”. Our algorithm would not identify them as people with active asthma. However, in these cases, the negative result is evidence that the subjects can achieve values for bronchial responsiveness within the healthy range, and could be interpreted as evidence that the person either no longer has the active disease or has responded well to treatment. It needs to be determined what is the chance of a person with documented mild asthma having a sustained attack that causes their temporary or permanent removal from the workplace before the true financial cost of allowing these “false negatives” into the ADF is known. As the cost of acute treatment to reverse an attack of asthma with a $\beta_2$-adrenoceptor agonist and the cost of treatment to gain control of asthma with inhaled corticosteroids is low, it is arguable that the exclusion of such individuals is unnecessary. This is beyond the scope of this article, but could be addressed by those who utilise the algorithm.

Our primary objective is to identify the problems with BPTs for occupational assessment in current practice and to propose a new direction. The new direction suggested in this proposal will be enhanced if the outcomes are carefully monitored and evaluated along the way. With a high prevalence of symptomatic asthma in Australia, there is potential for a significant number of people to be unfairly included or excluded from the workplace simply on the basis of a response to a questionnaire. Identifying these people by measurement of bronchial responsiveness to an indirect challenge at the point of occupational recruitment may be an important step forward to resolving this problem.

**Acknowledgement**

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