Review

Are non-allergenic environmental factors important in asthma?

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Abstract

Objective: To review the roles of viral respiratory tract infections, environmental tobacco smoke and air pollution in asthma.

Data sources: MEDLINE (1992–1995) searches were conducted for publications on asthma, environmental tobacco smoke, ozone, nitrogen dioxide and particulates.

Study selection: Representative original experimental and epidemiological studies and reviews of viral infections in asthma.

Data synthesis: Respiratory virus infections are the most common and important trigger of asthma attacks in children and probably also in adults. Their role in promoting development of asthma is not so clear. Exposure to environmental tobacco smoke is almost certainly responsible for some cases of childhood asthma, and can also trigger symptoms of bronchoconstriction in adults with asthma. Exposure to ozone or nitrogen dioxide is associated with symptoms, impaired lung function, bronchial hyperresponsiveness and hospital presentations for asthma. These pollutants may also act as cofactors in the development of allergen-specific bronchial hyperresponsiveness.

Conclusions: Research on preventing upper respiratory viral infections may reduce asthma morbidity. The move to non-smoking workplaces is welcome, but new interventions are needed to prevent young women taking up smoking and subsequently exposing their children. The ambient air quality guideline for ozone should be revised and a health-based guideline for respirable particulates introduced.

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Asthma is a major public health problem in Australia, affecting 13%–24% of children and 7%–13% of adults (depending on the definition used). Atopy, or the ability to mount IgE responses to environmental allergens, is clearly the major risk factor.[1] Yet atopy and allergen exposure alone are not responsible for all cases. Increasing attention is being paid to environmental factors other than allergens that may be involved either in the development of non-occupational asthma *de novo*, or in triggering attacks in pre-existing asthmatics. This review will focus on the roles of viral respiratory tract infections, environmental tobacco smoke and air pollution. Other environmental factors, such as diet, are beyond its scope.

Viral respiratory tract infections

Viruses as triggers of asthma

Epidemiological studies have shown that viruses are commonly associated with wheezing illnesses in populations, in individuals and in cohorts followed longitudinally. Viruses, unlike bacteria, are rarely found in patients during asymptomatic periods. They have been identified by conventional methods (viral culture, serology and immunofluorescent microscopy) in up to 50% of wheezing illnesses and asthma exacerbations in childhood and in up to 20% of those in adults.[2] In a recent study, which used the polymerase chain reaction to increase sensitivity to detect rhinoviruses and coronaviruses, viruses were identified in 80% of symptom episodes in schoolchildren — 66% were rhinoviruses and 16% coronaviruses.[3]

Wheezing occurred in over 50% of respiratory viral infections in people with asthma followed prospectively, and appeared more common if the infection was caused by rhinovirus and respiratory syncytial virus (RSV) in children presenting spontaneously with respiratory infections.[2] However, the few available adult studies show little association between particular viruses and wheezing, possibly as the predominant viruses causing respiratory infections change with age.[2] Children with asthma seem more prone to symptomatic viral infections than others, although this does not appear to be caused by atopy alone.[2]

Viruses are clearly important triggers of asthma exacerbations, and new approaches to prevention and treatment of viral infections could greatly reduce asthma morbidity.

Viruses as promoters of asthma

The role of viruses in the development of asthma and allergy is much less clear than their role in triggering asthma attacks.

Many studies seem to have documented a relationship between viral infections in infancy and later asthma symptoms, bronchial hyperresponsiveness and reduced lung function.[4] However, recent studies have shown that allergic sensitisation is less common in groups that have more early respiratory virus infections (as a result of factors such as hygiene and family size).[5] There is increasing evidence that infants who have recurrent wheezing with upper respiratory infections, improving by age 3–4 years, have congenitally small airways.[6] Consequently, the apparent association between early respiratory illness and later poor lung function may have resulted from biased selection of children with congenitally small airways.

Environmental tobacco smoke

Evidence is accumulating from hospital case–control and population studies for a link between exposure to environmental tobacco smoke and symptoms and diagnoses of asthma in children.[7-11] The association is strongest for asthma requiring regular treatment[7] and in young children,[7,11] but is also seen in those of school age.[10,11] Most studies have shown that the main risk factor is maternal smoking, and in the United States an estimated 7.5% of cases of symptomatic childhood asthma are attributed to this exposure.[11] In one case–control study, the risk was confined to non-allergic children.[9] Most studies used questionnaires to assess tobacco smoke exposure, but some have confirmed exposure by measuring salivary cotinine levels.[8]

Abnormal bronchial hyperresponsiveness has been linked to parental smoking during pregnancy for both infants[12] and older children,[13] but there is no consensus as to whether exposure to environmental tobacco smoke after birth has an effect.[8,14] However, this exposure does worsen asthma in children with the disease — it is linked to more frequent exacerbations, more peak flow variability in non-atopic subjects,[15] poorer lung function[16] and increased bronchial hyperresponsiveness.[17]

Among adults, the role of environmental tobacco smoke as a risk factor for asthma has not been extensively studied. Data from population studies linked this exposure to symptoms of "obstructive respiratory disease", but did not distinguish asthma.[18] A recent study showed a small increase in risk of "physician-diagnosed asthma" in never-smokers who reported exposure to environmental tobacco smoke at home or work.[19] Studies of short term exposure to tobacco smoke showed that some patients with asthma experience acute, reversible, dose-dependent decrements in lung function, although many do not react.[20,21]

Air pollution

The evidence for associations between respiratory disease and air pollution has been reviewed previously.[22,23] We will concentrate on recent evidence for adverse effects of the most common pollutants in Australian cities: ozone (O_3), nitrogen dioxide (NO_2) and respirable particles. The high levels of sulfur dioxide (SO_2) and acid aerosols seen in Europe and North America do not occur in Australia.

Photochemical smog

Photochemical smog is formed by a series of reactions involving oxides of nitrogen and related organic compounds, under the influence of solar ultraviolet radiation.[22] The principal constituents are ozone and nitrogen dioxide.

Experimental studies: Results of recent experiments on gaseous pollutants are summarised in the Table. Complex protocols with more than one pollutant and durations of exposure up to 6.5 hours are now being used to simulate real-world exposures. Increasingly, investigators are performing bronchoscopy with bronchoalveolar lavage to investigate inflammatory reactions within the lung, often at levels of exposure below those that cause physiological changes or symptoms.

There is now ample experimental confirmation that ozone causes reversible impairment of lung function after 2.33 hours' exposure at a level of 0.12 ppm, and that results of early studies on white men can be generalised to women and blacks.[24] In subjects with asthma, bronchoalveolar lavage shows neutrophilia and increased cytokine levels after exposure to ozone,[26] but the clinical significance is unknown and ozone appears not to potentiate exercise-induced asthma.[25]

A meta-analysis of 20 studies of subjects with asthma and five of healthy subjects confirmed that non-specific bronchial hyperresponsiveness increased significantly after resting exposure to nitrogen dioxide at levels as low as 0.1 ppm.[33] Pre-exposure to nitrogen dioxide, which occurs naturally during summer smog episodes, also potentiates the airway response to ozone.[28] However, the secondary pollutants — nitric acid and sulfuric acid — appear to have little additional effect.[29,30]

Epidemiological studies: Recent epidemiological studies suggest that photochemical smog has adverse health effects at relatively low levels of ozone and nitrogen dioxide. Temperature and ambient ozone levels accounted for 13%–15% of the variability in daily asthma visits to hospital emergency departments in New Jersey.[34] We were able to explain 23% of the variance in Victorian asthma admissions with a statistical model incorporating levels of ozone (which explained 13%), airborne particles and nitrogen dioxide, day of the week, presence of a northerly wind, and pollen counts.[35] In Finland, emergency attendances for asthma were predominantly related to levels of nitrogen dioxide, after allowing for the effects of temperature.[36] However, as these essentially ecological studies have significant limitations, it cannot be concluded that hospital admissions are caused by ozone alone.

The longer term respiratory effects of photochemical smog are still largely unknown, despite cross-sectional and longitudinal epidemiological studies. Bronchial hyperresponsiveness among schoolchildren was significantly greater in an area where 10% of ozone measurements exceeded 0.10 ppm than in an area with a maximum of 0.095 ppm.[37] A cohort study of children from Mexico City found that a 0.053 ppm rise in ambient ozone caused more frequent cough or phlegm and modest, but significant, impairments in lung function.[38] On the other hand, rising asthma mortality in Philadelphia was related to changes in ethnic mix, proportion of females and poverty levels, rather than air quality, which has improved significantly since 1965.[39]

Experiments on pulmonary responses to gaseous pollutants

Pollutant concentration	Numbers of subjects		Duration of exposure (hours)	Outcome measures	Conclusions
	Healthy	Asthmatic			
O_3 (0.12, 0.18, 0.24, 0.3, 0.4 ppm)[24]	372	—	2.33	FEV_1, SR_{aw}, cough	No significant sex or racial differences
O_3 (0.1, 0.25 ppm)[25]	—	21	1	FVC, FEV_1, exercise test	No significant potentiation of exercise-induced asthma
O_3 (0.2 ppm)[26]	5	5	6	BAL cell counts and cytokine levels	BAL neutrophilia and increased levels of interleukins 6 and 8
O_3 (0.12 ppm)[27]	—	7	1	Bronchial hyperresponsiveness to pollen	Increased hyperresponsiveness to allergen
O_3 (0.3 ppm) NO_2 (0.6 ppm)[28]	21 (women)	—	2	FVC, FEV_1, SR_{aw}, bronchial hyperresponsiveness to methacholine	NO_2 potentiated airway response to ozone
O_3 (0.2 ppm) HNO_3 (500 $\mu g/m^3$)[29]	10	—	4	FVC, FEV_1, SR_{aw}, BAL cell counts and protein levels	HNO_3 did not potentiate inflammatory response to O_3
O_3 (0.12 ppm) H_2SO_4 (100 $\mu g/m^3$)[30]	15	30	6.5	FVC, FEV_1, bronchial hyperresponsiveness to methacholine, symptoms	O_3 (and to lesser extent H_2SO_4) reduced lung function and increased bronchial hyperresponsiveness
NO_2 (0.1, 0.4 ppm)[31]	—	10	1	Bronchial hyperresponsiveness to house dust mite	NO_2 potentiated early and late asthmatic reactions
NO_2 (0.4 ppm) SO_2 (0.2 ppm)[32]	—	10	6	FVC, FEV_1, bronchial hyperresponsiveness to house dust mite	NO_2 and SO_2 together increased reactivity to allergen

ppm = parts per million. BAL = bronchoalveolar lavage. FVC = forced vital capacity. FEV_1 = forced expiratory volume in one second. SR_{aw} = specific airway resistance.

Interaction with allergens

There is recent experimental evidence of interactions between gaseous pollutants and allergens. Specific bronchial hyperresponsiveness to allergens of ragweed or grass pollen is enhanced by pre-exposure to ozone[27] and to allergens of house dust mite by nitrogen dioxide, with or without sulfur dioxide.[31,32] However, without individual exposure data or more precise estimates of clinical effects, the public health significance is unclear.[40]

Particulate air pollution

Particulate air pollution consists of products of combustion and dust. Its effects probably depend on the local composition. Particles with a diameter less than 10 μm (measured as particulate matter < 10 μm, or PM_{10}) can enter the respiratory tract and are therefore the most biologically important.

Particulate pollutants have acute deleterious effects on patients with asthma. Among asthmatic children, the likelihood of symptoms worsening and some of the day-to-day variability in lung function are related to the level of particulate pollution.[41,42] In addition, the risk of hospitalisation for asthma is related to recent ambient PM_{10} levels,[43,44] although the risk is most evident in children and is not seen in the elderly with asthma.[45]

The role of long term exposure to particulate pollution as a cause of asthma is difficult to assess. A series of studies among predominantly non-smoking Seventh Day Adventist adults in California concluded that the incidence of new diagnoses of asthma over a 10-year period was related to long term ambient concentration of particulates.[46] However, the problems of interpreting ecological studies and the confounding effects of acute exposures mandate caution in accepting this conclusion.

Conclusions

Non-allergenic environmental factors are important risk factors in asthma, although the risk is difficult to quantify and non-allergenic and allergenic factors probably interact. Respiratory virus infections are the most common and important trigger of asthma attacks in children and probably also in adults, although their role in the development of asthma is not so clear. Research directed at preventing these infections or ameliorating their effects could reduce morbidity from asthma.

Exposure to environmental tobacco smoke is almost certainly responsible for some cases of childhood asthma, and can also trigger symptoms and reversible bronchoconstriction in some adults and children with asthma. In adults, environmental tobacco smoke exposure may have a role in non-specific respiratory symptoms, but its role in the genesis of asthma has not yet been established. The declining prevalence of smoking among men and the move to restrict smoking in places such as hospitals, workplaces and aircraft should be welcomed. However, we need to develop new public health strategies to prevent young women taking up smoking and subsequently exposing their children to environmental tobacco smoke before and after birth.

Asthmatics are probably no more susceptible to ozone than people without asthma. None the less, exposure to ozone at levels less than the current National Health and Medical Research Council guideline of 0.12 ppm is associ-

Royal Australasian College of Physicians' position statement on ambient air pollution[47]

- Current goals for carbon monoxide, nitrogen dioxide and sulfur dioxide offer an appropriate level of protection.
- The goal for airborne lead levels should be reduced in line with European recommendations.
- There is evidence that the current one-hour goal for ozone will not protect all members of the population from transient effects. A new goal, in terms of a three-hour maximum exposure, is needed.
- Air quality goals should be introduced for respirable particulates.

ated with neutrophilic bronchial inflammation, reversible changes in lung function, bronchial hyperresponsiveness, asthma symptoms and hospital presentations. Nitrogen dioxide potentiates the bronchial effects of ozone and appears to increase bronchial hyperresponsiveness in asthmatic subjects. Both ozone and nitrogen dioxide may enhance allergen-specific bronchial hyperresponsiveness, although this requires further study. Particulate air pollutants also have acute deleterious effects on patients with asthma. The longer term respiratory effects of air pollution are still uncertain.

After reviewing this evidence, a number of professional bodies have produced position papers on ambient air pollution. The position statement of the Royal Australasian College of Physicians[47] is summarised in the Box. Despite these recommendations and five years of consideration by various Australian authorities, the ozone guideline has not been revised, nor has a health-based PM_{10} guideline been introduced.

Finally, when advising patients about environmental exposures that may influence asthma, doctors need to balance the likely benefits of avoidance against costs and inconvenience.

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