

Advances in adult asthma 2006: Its risk factors, course, and management

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This Advances article updates our understanding of risk factors for asthma and its course and management. Studies relevant to clinical practice are discussed, with special attention to their clinical research methods. (J Allergy Clin Immunol 117:1-10, 2006.)

Key words: Asthma, adults, health disparities, therapeutics, adherence

As in previous Advances,¹⁻³ the focus of this year's review is risk factors for asthma, its course, and management. Key advances are summarized in Table I. This year, Asthma Advances is in 2 parts: this article focuses on adults, whereas Szefer⁴ reviews pediatric advances in this issue of the Journal. This evaluation of new adult research will consider some clinical research problems that must be addressed to obtain meaningful results.

In formulating a study question, investigators must make methodologic choices that ultimately affect the validity and generalizability of their results. Two choices that might be particularly relevant and also difficult for asthma research are of study design and subject selection. With respect to study design, it may be impractical to use a longitudinal cohort or a randomized intervention for evaluating the relationship of asthma and obesity, for example, or whether certain fetal exposures are risk factors for asthma. Cross-sectional designs, more feasible, can be used to describe whether variables measured at one time point are statistically associated. However, they cannot determine whether one variable chronologically preceded another or whether a cause-and-effect relationship exists among variables. Nevertheless, they may be useful for generating hypotheses for further investigation.

The method by which subjects are selected can also influence the outcome. Recruiting persons with self-reported asthma is convenient and sensitive, but not necessarily specific, as individuals with asthma symptoms

Abbreviations used

FENO: Fraction of exhaled nitric oxide

ICS: Inhaled corticosteroid

such as cough, shortness of breath, or wheezing from other causes may be included. As most patients with asthma have mild disease and normal or near-normal spirometry, the extent to which they populate a study may influence its relevance to patients with more severe asthma. Thus, study design and patient selection are important methodologic issues and will be used to frame this review.

THE COURSE OF ASTHMA AND NEW RESEARCH ABOUT RISK FACTORS

Birth cohorts and the natural history of asthma

Reed⁵ thoughtfully reviewed the birth cohort studies concerning the natural history of asthma. He concludes that allergic asthma develops most frequently in the second decade, and when older individuals develop new allergic asthma, it is in response to a new allergen. Although many patients with allergic asthma experience transient or permanent remission, those with more severe asthma or asthma associated with continued allergen exposure are less likely to do so. In contrast, intrinsic asthma can develop at any age, but is more frequent, persistent, and severe in middle-aged and older adults. Such heterogeneity supports the theory that asthma is a complex disease to which many genes contribute. Heterogeneity also results from varied environmental factors, including occupational and social exposures, leading to gene-environment interactions. With regard to patient selection in birth cohort studies, Reed observes that significant numbers of asthmatic individuals have coexisting lung disease or develop asthma later in life.⁵ Neither group has been captured by birth cohorts, yet both have significant morbidity and deserve study.

Preterm delivery

Jaakkola et al⁶ conducted a meta-analysis questioning whether preterm birth (gestational age less than 37 weeks) is associated with development of asthma, defined by a physician's diagnosis, hospitalization, patient or parent report, or history of asthma. Nineteen original studies—14

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TABLE I. Key advances in adult asthma in 2006

1. Persistence or refill of ICS is poor.
2. Patients receiving combination rather than concurrent ICS and LABA refill slightly more frequently, if there is no cost differential.
3. Use of the lowest effective dose of ICS is warranted; ICS use in mild/moderate asthma compares favorably to other therapies assuming a wide range of assumptions about ICS's effect on bone density.
4. Asthma and obesity are statistically associated, but whether there is a causal relationship has not been determined.
5. In assessing the impact of environmental exposures on asthma, social variables must also be considered.
6. When reporting clinical outcomes, including biomarker assessments strengthens the research.

LABA, Long-acting β -agonist.

cohort, 4 cross-sectional, and 1 case-control—were identified. A 7% increase in risk was found in preterm children, but the risk was heterogeneous, with a stronger relationship found in cross-sectional studies, smaller studies, and studies with younger participants (perhaps the differences diminishing as infants' lungs mature).

Sex hormones

Sex hormones have been hypothesized to modulate asthma control, as asthma prevalence among females increases after puberty. Salam et al⁷ report a cross-sectional study examining whether early menarche among females of 13 to 28 years is associated with the onset of asthma after puberty and whether oral contraceptive (OC) use was linked to current wheeze. For this secondary analysis of data from the Children's Health Study, the investigators defined asthma as self-reported current or exercise-induced wheeze or the use of asthma medications. They found that women with menarche before age 12 years had a 2-fold higher risk of asthma after puberty, but 39% of the subjects from the original cohort could not be contacted and were excluded from their analysis. In women without asthma, OC use was associated with higher risk of wheeze, but among women with a history of asthma, OC use was related to a reduced risk of current wheeze. Among other possibilities, the investigators speculated that taking OCs motivate better adherence to asthma medications. These puzzling findings do not support a significant clinical relationship between female hormones and asthma.

Obesity

Obesity is statistically associated with asthma,⁸⁻¹² as has been discussed in this Journal previously.¹³⁻¹⁹ What remains unclear is whether the association has a biologic cause, whether respiratory symptoms in obese persons are misdiagnosed as asthma, or whether the observed association is due to simultaneously occurring but unrelated factors, such as the growing availability of high-calorie food, but at the same time access to medical care of asthma is becoming more difficult for low-income patients. Several researchers have attempted to determine whether the link is an obesity-induced proasthmatic inflammatory state, as manifested by positive associations with atopic status²⁰ or IgE levels¹⁴ or by a negative association with exhaled nitric oxide (FENO).¹³ However, these studies are cross-sectional, and some use self-report to define asthma, emphasizing the need for longitudinal, prospective studies.

Social environment

Social environment has a marked influence on the outcome of asthma and other treatable diseases.^{21,22} Low socioeconomic status is a major risk factor for death from asthma,⁵ as is membership in certain racial and ethnic minority groups.²² As noted by Joseph et al,²³ emergency department rates, hospitalizations, and deaths from asthma are 2 to 4 times higher in African Americans than whites. The highest asthma prevalence is reported in Puerto Rican Americans (13.5%), followed by Native Americans (9.9%), non-Hispanic blacks (9.5%), and whites (7.2%). Addressing barriers to quality of care related to access, socioeconomic status, culture, physical environment, and genetic susceptibility is arguably today's most important task for asthma clinical researchers, health policy experts, and physicians caring for patients.^{21,23,24} The research cannot come too soon, because as Gupta et al²⁵ point out in their cohort study using data from the National Hospital Discharge Survey US, the black/white differences in hospitalizations and mortality are increasing for children between 5 and 18 years.

The hygiene hypothesis

The hygiene hypothesis, discussed in previous Advances,^{1,3} continues to generate controversy. Using data from the third National Health and Nutrition Examination Survey (NHANES III), Arbes et al²⁶ found colonization of the oral cavity by bacteria (measured indirectly by examining serum IgG directed against these micro-organisms) associated with asthma, wheeze, and hayfever. In Vietnamese schoolchildren, sensitization to dust mite was negatively associated with hookworm burden and *Ascaris* infection and positively associated with use of flush toilets.²⁷ Radon and Schulze²⁸ explored the relationship of obesity and non-farm living as Western lifestyle markers with rhinitis symptoms and allergic sensitization. Although interesting, as noted by the authors described above and in a commentary by Gold,²⁹ such findings are limited by their cross-sectional designs and the possibility of unmeasured confounders. Two reports are also limited by the use of self-report for diagnosis of asthma.^{30,31}

MEASURING ASTHMA CONTROL

Asthma control, an important variable in clinical studies, may be measured by self-report, biomarkers, or

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