Foreword

Environmental Factors in Asthma

Rafeul Alam, MD, PhD
Consulting Editor

Whether you take the biblical quotation—“for dust you are and to dust you will return” (Genesis 3:19)—or the theory of evolution, which implies that environmental changes triggered the biological evolution, it is all about environment. We as biologists have recognized the power of genes ever since Mendel demonstrated the principles of genetic inheritance, and Watson and Crick resolved the structure and beauty of the double helix. The driving power of genes in the expression of a phenotype is undeniable. Nonetheless, phenotype is not the same as genotype, and we are yet to fully understand the complexity of the gene–environment interaction. Our simple paradigm of promoter-driven exon-based gene expression is losing its ground. We now understand that the expression of a gene is far more complex. Gene expression is controlled by proximal and distant enhancers and silencers, epigenetic modulation of the gene locus, secondary regulation by microRNA, gene splicing, single nucleotide polymorphism, and other factors. Many of the foregoing processes are influenced by the environment.

Asthma, being a polygenic disease, is far more susceptible to environmental changes. Thus, research in the environmental aspect of asthma is very important. A comprehensive understanding of the environmental contribution to asthma requires population-based case control and prospective epidemiologic studies, which are extremely difficult to conduct. Nonetheless, significant progress has been made in this field. We have observed continued evolution of the hygiene hypothesis. We have a better understanding of
indoor pollution. We recognize the complex biologic effect of indoor allergens. To elaborate on the complexity of environmental factors, Dr. Mark Eisner, a leader in the field, has invited some of the top experts to contribute to this issue. The issue addresses such important areas as indoor allergens, indoor and outdoor pollution, hygiene hypothesis dealing with microbial environment, social environment that includes diet and obesity, and others. This will be an exciting reading.

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Preface

Mark D. Eisner, MD, MPH
Guest Editor

The morbidity and mortality from asthma have increased greatly during the past few decades in the United States and most developed countries. Although recent developments in genetics have provided exciting breakthroughs in airway disease, genetic factors, by themselves, cannot explain the dramatic increases in asthma prevalence and severity. Dramatic changes in the environment have occurred concurrently with the asthma epidemic, raising the possibility that environmental factors may be responsible for the increased burden of asthma. Indeed, the alterations of the indoor and outdoor environment are dramatic features of the twentieth and twenty-first centuries. Changes in diet, body composition, and workplace conditions have also occurred. In this issue of the *Immunology and Allergy Clinics of North America*, we review recent epidemiologic studies that implicate the environment as a cause of asthma and its exacerbation.

The term “environment” is broad and all encompassing. Indeed, it reflects all that is external to the human organism. For many, the term “environment” connotes the outdoor environment and its pollution by traffic, other sources of combustion, and industrial contamination. But for most residents of industrialized countries, the majority of time, in excess of 90%, is spent indoors. Consequently, the indoor environment, which includes homes, schools, workplaces, and other public places, becomes especially important. Although it is true that the outdoor (ambient) environment greatly influences the indoor one by entrainment of air and other substances, there are unique point sources of pollution, allergen exposure, and viral infection indoors. And finally, the social environment, which...
reflects the broader context of our lives, may have important influences on asthma.

Randomized controlled trials have become the gold standard for addressing many problems in clinical medicine and health. But such trials are not suited to studying most of the effects of environmental exposures on health. Although short-term exposure studies are conducted in highly controlled environments, they provide limited insight into the development of chronic diseases such as asthma, which have a long induction period (ie, develop over a long period of time). Ethical and logistic concerns preclude randomizing human subjects to potentially hazardous exposures over a longer time period. Therefore, epidemiologic methods are the best ones for assessing the impact of environmental exposures on health outcomes, such as asthma and other respiratory diseases.

In this issue, we review the evidence that exposures to indoor pollution (passive smoking, indoor combustion), other indoor exposures (allergens, viral infections, occupational exposures, dampness, mold), and outdoor pollution (traffic, other ambient pollution) are important factors for the development and clinical course of asthma. The issue also considers the social environment and how it influences asthma status. The impact of diet and obesity, which have changed markedly during the past several decades, may also contribute substantively to the asthma epidemic. And living on a farm, with exposure to microbes and allergens, has fascinating, and sometimes counterintuitive, effects on asthma induction and course. Finally, an article on asthma and the inner city integrates the issues of pollutant and allergen exposure that often occur concurrently in the urban environment.

Ultimately, the goal of epidemiology and public health is prevention—in this case, prevention of asthma incidence and exacerbation. This issue elucidates the impact of the environment, defined broadly, on asthma with the goal of highlighting possible areas in which exposure prevention or remediation might decrease the burden of asthma.

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Dampness and Mold in the Indoor Environment: Implications for Asthma

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The National Institute for Occupational Safety and Health receives weekly requests to help with issues of indoor environmental quality in relation to illness in nonindustrial workplaces, such as office buildings and schools. Since the mid-1990s, there has been a marked increase in the number of these requests to the point where in 2007 they represented 57% of the total of 390 requests for evaluation of the workplace in relation to health and safety issues. As an example of requests concerning work-related asthma, from January 2007 through December 2007, there were 39 requests in relation to asthma, 34 (87%) from nonindustrial workplaces with workers concerned about indoor environmental quality. Of these 34 requests, 23 (68%) listed dampness or mold as exposures of concern. Thus, asthma in the nonindustrial environment accounts for the majority of the public’s concern for possible work-related asthma, and requesters have made the association between their work-related asthma symptoms and damp/moldy environments. A recent calculation estimates that 21% (95% confidence interval [CI], 12%–29%) of current asthma in the United States is attributable to dampness/mold in homes [1].

This article presents epidemiologic findings pertinent to asthma and asthma-like symptoms in relation to exposure to dampness/mold in homes, schools, and workplaces. With regard to specific agents found in damp indoor environments that may play a role in asthma, it concentrates on mold (used synonymously with fungi) and includes some findings on bacteria. The literature on asthma in relation to dust mite or cockroach allergens is not addressed.

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Reviews of the epidemiologic literature up to 2003

A European review (NORDDAMP) of well-designed epidemiologic studies published prior to July 1998 found that odds ratios (ORs) for cough, wheeze, and asthma associated with indoor dampness ranged from 1.4 to 2.2 [2]. A subsequent review (EUROEXPO) of studies published from 1998 to 2000 confirmed indoor dampness as a risk factor for health effects, regardless of atopic status. The investigators concluded that additional prospective studies were needed [3].

In the United States, the Centers for Disease Control and Prevention asked the Institute of Medicine (IOM) to complete a review of the scientific literature. The IOM committee reviewed studies published up to late 2003 believed influential in shaping the scientific understanding of dampness-associated health effects [4]. With respect to asthma and asthma-related symptoms, the IOM found that there was sufficient evidence for associations between exposure to damp indoor environments or mold or other agents in damp indoor environments and cough, wheeze, and asthma symptoms in asthmatic persons, and limited or suggestive evidence for associations with asthma development and dyspnea. They concluded that excessive indoor dampness is a public health problem and that prevention or reduction of this condition should be a public health goal. Among the research needs formulated by the committee were improved characterization of dampness-related microbial emissions and chemical emissions from building materials and furnishings and their roles in adverse health outcomes; studies on interaction effects of multiple exposure factors in damp indoor environments; and studies on intervention effectiveness.

Meta-analysis in 2007

A meta-analysis of 33 peer-reviewed epidemiologic studies on respiratory health outcomes and home dampness or mold included studies published from 1989 to 2006 [5]. The estimated OR for cough in adults was 1.52 (95% CI, 1.18–1.96); for cough in children 1.75 (95% CI, 1.56–1.96); for wheeze in adults 1.39 (95% CI, 1.04–1.85); for wheeze in children 1.53 (95% CI, 1.39–1.68); for current asthma 1.56 (95% CI, 1.30–1.86); for ever-diagnosed asthma 1.37 (95% CI, 1.23–1.53); and for asthma development 1.34 (95% CI, 0.86–2.10). The investigators estimated that home dampness or mold is associated with a 30% to 50% increase in respiratory health outcomes.

Dampness/mold and asthma development—recent publications

Recent research not included in the 2004 IOM report has increased the body of evidence regarding the association between dampness and asthma development (Tables 1 and 2).
In a study that investigated occupational exposures, researchers reviewed medical records at clinics in a Swedish town covering a 1.5-year period to identify cases of newly diagnosed asthma among 20 to 65 year olds [6]. Controls were randomly selected from the Swedish population registry, lived in the same town, and were matched by age and gender to cases. Response rates and study numbers for cases and controls were 90% (n = 120) and 84% (n = 446), respectively. The OR (adjusted for occupational exposure to dust, fumes, or vapors, childhood allergy symptoms, and ever smoking) for workplace exposure to building mold or moisture damage that lasted 3 or more years and occurred before the year of asthma diagnosis (for cases) or referent time (for controls) was 4.7 (95% CI, 1.5–14.3). Because this study included agricultural and maintenance workers whose exposure may differ in intensity and type from office workers in damp buildings, caution should be exercised when applying these findings to workers of nonindustrial indoor environments.

A study by Gunnbjörnsdóttir and colleagues used data from the 1990–1994 European Community Respiratory Health Surveys (ECRHS) and a follow-up survey conducted in 1999–2001 [7]. Participants from four Nordic countries were 20 to 44 years old at the time of the initial survey. Response rates and study numbers for the initial and follow-up surveys were 84% (n = 21,802) and 74% (n = 16,190). New-onset asthma was defined as an asthma attack or use of asthma medications during the past 12 months on the second survey with negative responses to both of these questions on the first survey. The OR (adjusted for age, study center, gender, body mass index, rhinitis, smoking status, type of housing, age of building, and socioeconomic status) for the association between the presence of home dampness anytime between the two surveys and new-onset asthma was 1.13 (95% CI, 0.92–1.40) and thus did not quite meet statistical significance. Associations for new-onset asthma symptoms were significant. Researchers also investigated the remission of asthma-like symptoms and found that presence of home dampness between the two surveys significantly decreased remission of nocturnal dyspnea and nocturnal cough. Analysis of a subset (Swedish subjects, n = 1854) of second survey, also by Gunnbjörnsdóttir and colleagues, participants demonstrated significant positive associations between home dampness and dyspnea at rest, dyspnea after exertion, and nocturnal dyspnea [8].

A Finnish population-based incident case-control study compared 521 adults, who had newly diagnosed asthma (defined as reversible airways obstruction with at least one asthma-like symptom) identified over a 2.5-year period, to 932 randomly selected controls who did not have asthma [9]. Response rates for cases and controls were 90% and 80%, respectively. Cases and controls were 21 to 63 years old and lived within the same hospital district in South Finland. Workplace wall-to-wall carpeting and workplace mold independently increased the risk for new-onset asthma.
Table 1
Epidemiologic studies investigating an association between indoor dampness or mold and new-onset asthma or new-onset asthma-like symptoms that use odds ratios as a measure of risk

<table>
<thead>
<tr>
<th>Reference</th>
<th>Study design</th>
<th>Environmental exposure</th>
<th>Health outcome</th>
<th>Odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Adults</strong></td>
<td></td>
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<tr>
<td>Flodin and Jönsson [6]</td>
<td>Longitudinal case-control study (20–65 years old)</td>
<td>Reported workplace dampness (mold or moisture damage)(^b)</td>
<td>New-onset physician-diagnosed asthma at age 20–65 years</td>
<td>4.7 (1.5–14.3)</td>
</tr>
<tr>
<td>Gunnbjörnsdóttir et al [7]</td>
<td>Prospective study with a 7.9-year follow-up period (mean age at follow up: 40 years)</td>
<td>Reported dampness (water damage, leakage, or mold growth) in the home(^b)</td>
<td>New-onset asthma attack or current use of asthma medications(^c)</td>
<td>1.1 (0.9–1.4)</td>
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<tr>
<td></td>
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<td>New-onset wheeze(^c)</td>
<td>1.3 (1.1–1.5)</td>
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<td></td>
<td>New-onset nocturnal dyspnea(^c)</td>
<td>1.3 (1.1–1.6)</td>
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<td></td>
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<td></td>
<td>New-onset nocturnal cough(^c)</td>
<td>1.3 (1.1–1.4)</td>
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<tr>
<td>Jaakkola et al [9]</td>
<td>Population-based incident case-control study (21–63 years old)</td>
<td>Reported visible mold or mold odor at work(^c) and – No wall-to-wall carpet at work – Wall-to-wall carpet at work</td>
<td>New-onset physician-diagnosed asthma with both reversible airways obstruction and a history of at least one asthma-like symptom</td>
<td>1.4 (0.9–2.1)</td>
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<tr>
<td><strong>Children</strong></td>
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<tr>
<td>Wickman et al [12]</td>
<td>Prospective study of a birth cohort from age 2 months to 2 years of age</td>
<td>Reported water damage, windowpane condensation, visible mold, or mold odor when child was 2 months of age</td>
<td>Three or more episodes of wheezing after age 3 months and either use of inhaled steroids or symptoms suggestive of bronchial hyper-reactivity</td>
<td>1.7 (1.3–2.4)</td>
</tr>
<tr>
<td>Emenius et al [13]</td>
<td>Nested case-control study of a birth cohort (2 years old)</td>
<td>One sign of dampness based on home inspection Three or more signs of dampness based on home inspection</td>
<td>Three or more episodes of wheezing after age 3 months and either use of inhaled steroids or symptoms suggestive of bronchial hyper-reactivity</td>
<td>1.3 (0.8–2.2)</td>
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<td>Description</td>
<td>Value</td>
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<td>----------------------------------------------------------------------------</td>
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<td>Mold odor based on current home inspection</td>
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<td>Visible mold based on current home inspection</td>
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<td>Visible mold in main living area based on current home inspection</td>
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<tr>
<td>Water damage in main living area based on current home inspection</td>
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<tr>
<td>New-onset physician-diagnosed asthma or new referral to hospital after two or more attacks of wheezing</td>
<td>4.1 (0.6–26.0)</td>
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<td></td>
<td>1.2 (0.7–2.1)</td>
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<td>2.6 (1.2–5.8)</td>
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<td></td>
<td>2.2 (1.2–4.0)</td>
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</tbody>
</table>

a Present for 3 or more years and occurred at least 3 years before year of asthma diagnosis.
b Present any time in between the initial and follow-up survey.
c Present during the past year.
Table 2
Epidemiologic studies investigating an association between indoor dampness or mold and new-onset asthma that use incidence rate ratio as a measure of risk

<table>
<thead>
<tr>
<th>Reference</th>
<th>Study design</th>
<th>Environmental exposure</th>
<th>Incidence rate ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Adults</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cox-Ganser et al [10]</td>
<td>Cross-sectional study with information on dates of hire and asthma diagnosis (mean age 46 years)</td>
<td>Office building with water damage and mold contamination based on building inspection</td>
<td>7.5 (no CI)</td>
</tr>
<tr>
<td>White et al [11]</td>
<td>Cross-sectional study with information on dates of hire and asthma diagnosis (mean age 48 years)</td>
<td>School building with evidence of water damage and mold contamination based on building inspection</td>
<td>8.5 (no CI)</td>
</tr>
<tr>
<td><strong>Children</strong></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>
| Jaakkola et al [14] | Population-based cohort study with a 6-year follow-up period (1–7 years old at baseline) | Reported mold odor in the home<sup>b</sup>  
Reported visible mold in the home<sup>b</sup>  
Reported moisture on surfaces in the home<sup>b</sup>  
Reported water damage in the home<sup>b</sup>  
Any of above dampness indicators | 2.4 (1.1–5.6)  
0.6 (0.2–1.7)  
0.9 (0.5–1.5)  
1.0 (0.4–2.3)  
1.0 (0.7–1.5) |


<sup>b</sup> Present during the past year at time of initial survey.
Workplace wall-to-wall carpet together with workplace mold further increased the risk for new-onset asthma. Results were adjusted for gender, age, education, personal smoking, environmental tobacco smoke, water damage, and damp spots at home. It is possible that carpets acted as a reservoir for moisture and related contaminants.

Two cross-sectional studies of United States office and school employees who worked in buildings with water damage and mold contamination found postoccupancy adult-onset asthma incidence densities to be 7.5 and 8.5 times greater than preoccupancy incidence densities, respectively [10,11]. Although, incidence rate ratios (IRRs) were not adjusted for demographic variables, pre- and postoccupancy asthma incidence densities were calculated for the same group of participants. These studies support a temporal association, which is important in establishing a causal association of exposure with disease.

**Children**

A birth cohort study of 4089 Swedish children at 2 months old and 1 and 2 years old found a positive association between damp home environment and asthma development 1.74 (95% CI, 1.28–2.39), adjusted for gender, parental history of allergic disease, socioeconomic status, maternal age, exclusive breastfeeding, maternal smoking, pet ownership, and age of building [12]. Data on damp home environment were taken from the first questionnaire when the children were 2 months old. Asthma was defined as at least three episodes of wheezing between 3 months and 2 years of age, in combination with treatment of inhaled glucocorticoids or signs of hyperreactivity without upper-respiratory infection. In a subsequent nested case-control study of the same birth cohort, 181 children who met the case definition were compared to 359 age-matched healthy controls [13]. Information on damp indoor conditions came from the baseline questionnaire and from home inspections in the first winter season after recruitment into the case-control study. There were consistent positive associations between indicators of dampness/mold in the home and being a case. A strong finding was that there was an increasing risk for recurrent wheezing with an increasing number of indicators of dampness found during the home inspections: one indicator of dampness was associated with an OR of 1.3 (95% CI, 0.8–2.2), whereas having three or more dampness indicators was associated with an OR of 2.7 (95% CI, 1.3–5.4).

A cohort study of randomly selected children from the Finnish population registry used results from a survey at age 1 to 7 years and another survey 6 years later [14]. Response rates and study numbers for the initial and subsequent surveys were 80% (n = 2568) and 77% (n = 1984), respectively. Children were considered exposed if mold odor, visible mold, dampness, or water damage had been reported in the home prior to the baseline study. The IRR for asthma comparing children exposed (n = 384) and nonexposed
(n = 1532) to mold odor was 2.44 (95% CI, 1.07–5.60) after adjustment for age, gender, duration of breastfeeding, parental education, single parent, maternal smoking during pregnancy, environmental tobacco smoke exposure, gas cooking, presence of furry or feathery pets, and type of child care. One of the major strengths of this study was its prospective study design, which eliminated over-reporting of pre-existing home mold based on newly diagnosed asthma and provided evidence for a temporal relationship between home mold and asthma.

Other Finnish researchers conducted a case-control study of children newly diagnosed with asthma at the university hospital in Kuopio, Finland [15]. Cases were defined as children 1 to 7 years of age who had been referred to the hospital because of two or more attacks of wheezing within the past year or were newly diagnosed with asthma. Controls who did not have asthma were randomly drawn from the Finnish population registry and matched by age, gender, and municipality to cases. Cases and controls were required to have lived at least 2 years or at least 75% of their lifetime in their current homes. Participation rates and study numbers for cases and controls were 98% (n = 121) and 84% (n = 241). Homes were inspected for evidence of mold odor, visible mold, and water damage. Models adjusted for parental asthma, paternal education, number of siblings, indoor pets, and daycare attendance during the first year of life yielded significant results for water damage in the main living area (OR 2.24; 95% CI, 1.25–4.01) and visible mold in the main living area (OR 2.59; 95% CI, 1.15–5.85). The study found a trend for increased risk for newly diagnosed asthma with each additional square meter of observed home water damage (OR 1.36; 95% CI, 0.91–2.03).

Dampness/mold and dyspnea—recent publications

Recent studies have investigated associations with dyspnea, nocturnal dyspnea, dyspnea during exertion, dyspnea after exertion, and dyspnea at rest, with differing results. The findings of Gunnbjörnsdóttir and colleagues in relation to dyspnea were discussed previously. Park and colleagues developed a grading system for visible water stains, visible mold, mold odor, and moisture, which they applied in an investigation of 1231 employees (mean age 51 years) of a United States community college that had several water-damaged buildings [16]. Dampness indicators in models adjusted for age, gender, smoking, job status, year of hire, allergies, and use of latex gloves were shown to predict risk for dyspnea present during the past 12 months that improved away from the building.

Others have compared the prevalence of work-related dyspnea among employees in water-damaged and mold-contaminated buildings to a United States survey of office workers in nonproblem buildings [10,17]. Work-related dyspnea was defined as shortness of breath that occurred 1 or more days per week in the past 4 weeks and which improved away from
work. Although analyses could not be controlled for demographic factors, researchers found significantly elevated prevalence rate ratios (2.2 to 4.6) that suggested an association between building dampness and dyspnea.

Researchers in Norway studied 2819 randomly selected adults, ages 26 to 81 years, who resided 11 years earlier (time of first survey) in the same county in Western Norway [18]. Response rate for the survey was 89%. In logistic regression models adjusted for age, gender, smoking status, educational level, pack years, and occupational exposure to dust or fumes, visible mold in the home significantly increased the risks for dyspnea when climbing two flights of stairs at an ordinary pace and of attacks of dyspnea (OR 2.3 [95% CI, 1.35–3.85] and 1.7 [95% CI, 1.06–2.72], respectively).

In summary, all nine studies (five adult studies and four pediatric studies) addressing environmental dampness and new-onset asthma published since the IOM report demonstrate some significant associations between environmental dampness and new-onset asthma or new-onset asthma-like symptoms. Additionally, all five adult studies investigating associations between environmental dampness and dyspnea found some significant associations between one or more measures of dyspnea and environmental dampness. Two of these studies showed an exposure-response relationship.

Microbial exposures in damp environments and asthma and asthma-like symptoms—recent publications

Recent research has advanced the knowledge on associations between asthma development or asthma-like symptoms and fungi and bacteria (Table 3). Limitations of sampling and analytic methods for microbial agents and lack of knowledge on which specific fungi or microbial agents are relevant measures of risk for respiratory illness have hampered exposure assessment. Such limitations include (1) lack of personal sampling methods for estimating long-term exposure to airborne microbes or microbial agents, (2) difficulty in accounting for the large temporal and spatial variability of airborne microbial agents with standard short-term sampling methods, (3) high sampling and analytic cost, and (4) lack of standardized analytic methods. Despite these limitations, measured exposure assessments are necessary to obtain evidence on possible etiologic agents of disease.

Adults

A longitudinal study of subjects who participated in the ECRHS in Melbourne, Australia, followed 360 adults (20 to 45 years old) over a 2-year period with regard to measured home exposures and the development and remission of asthma [19]. The investigators measured dust mite and cat allergens and ergosterol (the principal sterol in fungal membranes) in bedroom floor and bed dust samples and culturable fungi from bedroom air samples at the onset of the study and 2 years later. They found that
Table 3
Epidemiologic studies investigating an association between microbial agents and asthma and asthma-like symptoms

<table>
<thead>
<tr>
<th>Reference</th>
<th>Study design</th>
<th>Health outcome</th>
<th>Odds ratios</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Total fungi</td>
<td>Specific fungi</td>
</tr>
<tr>
<td>Matheson [19]a</td>
<td>Longitudinal study:</td>
<td>Development:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>home (20–45 y)</td>
<td>Current asthma</td>
<td>1.5 (a)</td>
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<tr>
<td></td>
<td></td>
<td>Asthma attack</td>
<td>1.5 (a)</td>
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<td></td>
<td></td>
<td>PD asthma</td>
<td>0.9 (a)</td>
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<td></td>
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<td>Remission:</td>
<td></td>
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<td></td>
<td></td>
<td>Current asthma</td>
<td>1.2 (a)</td>
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<td></td>
<td></td>
<td>Wheeze</td>
<td>1.0 (a)</td>
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<td></td>
<td></td>
<td>BHR</td>
<td>1.0 (a)</td>
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<tr>
<td>Park et al [20]b</td>
<td>Case-control study:</td>
<td>Post-occupancy</td>
<td>1.6 (fd)</td>
</tr>
<tr>
<td></td>
<td>office (mean age 46 y)</td>
<td>PD asthma</td>
<td>1.7 (cd)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PD asthma or asthma symptoms</td>
<td>1.6 (fd)</td>
</tr>
<tr>
<td>Park et al [21]c</td>
<td>Cross sectional study:</td>
<td>WR wheeze</td>
<td>2.0 (fd)</td>
</tr>
<tr>
<td></td>
<td>office (mean age 46 y)</td>
<td>WR chest-tightness</td>
<td>1.9 (fd)</td>
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<td></td>
<td></td>
<td>WR shortness of breath</td>
<td>2.4 (fd)</td>
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<td>WR cough</td>
<td>1.7 (fd)</td>
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<tr>
<td>Salo et al [22]c</td>
<td>Cross sectional study:</td>
<td>Current PD asthma</td>
<td>–</td>
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<tr>
<td></td>
<td>home (73% &gt; 18 y)</td>
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<tr>
<td><strong>Children</strong></td>
<td><strong>Birth cohort study: home (1–4 y)</strong></td>
<td><strong>PD asthma by age 4</strong></td>
<td><strong>Persistent wheeze in past 4 years</strong></td>
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<td><strong>Hyvärinen et al [27]</strong></td>
<td><strong>Case-control study: home (1–7 y)</strong></td>
<td><strong>Development of asthma</strong></td>
<td><strong>1.1 (Mes/hd)</strong></td>
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<td><strong>van Strien et al [28]</strong></td>
<td><strong>Cross-sectional study: home (6–14 y)</strong></td>
<td><strong>PD asthma</strong></td>
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<td><strong>Kim et al [29]</strong></td>
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ORs in bold font are significant for $P \leq 0.05$. Underlined ORs are marginally significant for $0.05 < P \leq 0.10$.  

**Abbreviations:** a, airborne; act, actinomycetes; Alt, Alternaria; bd, bed dust; BHR, bronchial hyper-reactivity; cd, chair dust; Cla, Cladosporium; EPS, extracellular polysaccharide of *Penicillium* and *Aspergillus* species; Erg, ergosterol; fd, floor dust; Glu, glucan; hd, house dust; Hyd, hydrophilic; Mes, mesophilic; mur, muramic acid; PD, physician-diagnosed; sd, surface dust; WR, work-related; Xer, xerophilic.  

* ORs are for twofold increase of exposure in the second survey compared to the first survey.  
* ORs are for IQR increase (cfu/g dust) in exposure.  
* ORs are for highest tertile compared to lowest tertile exposure group.  
* ORs are ratios are for high compared to low exposure group.  
* ORs are for each 0.01 nm/mg increase of endotoxin, $10^5$ cfu/g increase of mesophilic bacteria, $10^3$ cfu/g increase of mesophilic actinomycetes, $10^3$ pg/mg increase of ergosterol, $10^5$ cfu/g increase of mesophilic fungi, and $10^5$ cfu/g increase of xerophilic fungi.  
* ORs are for each $10^2/m^3$ increase of bacteria or mold and 1 µg/m$^3$ increase of total MVOC.
increase in exposure to airborne *Cladosporium* over the study period significantly increased the risk for an asthma attack (OR 1.52; 95% CI, 1.08–2.13). An increase in airborne total culturable fungi over the study period also increased the risk for an asthma attack (OR 1.54; 95% CI, 0.98–2.43) and the development of asthma (wheezing in the past 12 months with bronchial hyper-responsiveness) (OR 1.53; 95% CI, 0.93–2.53). Despite the use of short-term (1-minute) air samples for fungal measurements, positive associations were found. Conversely, although ergosterol levels in dust may better represent long-term exposure, the investigators found no associations.

A case-control study was nested within the cross-sectional study (discussed previously) of 888 participants working in a large water-damaged building in the United States where there was a large increase of postoccupancy adult-onset asthma [10,20]. Fungal exposures for 49 cases of current physician-diagnosed postoccupancy asthma and 152 controls (who had no lower respiratory and systemic symptoms and no physician diagnosis of asthma, hypersensitivity pneumonitis, or sarcoidosis) were compared using logistic regression models (adjusted for age, gender, race, smoking status, and building occupancy period). Researchers found postoccupancy asthma significantly associated with dust-borne total and hydrophilic (water-loving) culturable fungi (yeasts, *Phoma herbarum*, *Chaetomium globosum*, *Mucor plumbeus*, *Rhizopus stolonifer*, and *Stachybotrys chartarum*) in a linear exposure-dependent manner. Interquartile ranges (IQRs) were calculated by subtracting the 25th percentile values from the 75th percentile values. ORs for the risk for postoccupancy onset asthma per IQR of total culturable fungi in floor and chair dust were 1.6 (95% CI, 0.96–2.53) and 1.7 (95% CI, 1.07–2.60), respectively. ORs for the risk for postoccupancy asthma per IQR of hydrophilic fungi in floor and chair dust were 2.2 (95% CI, 1.23–3.89) and 1.9 (95% CI, 1.19–2.89), respectively. In a cross-sectional analysis using all 888 participants, the same floor dust samples (n = 338) analyzed for culturable fungi and endotoxin (the biologically active lipopolysaccharide found in the cell walls of gram-negative bacteria) were used to establish low-, medium-, and high-exposure categories [21]. Symptoms were defined as building related if they improved when away from the building. The investigators found that fungi and endotoxin in dust were significantly associated with building-related asthma-like symptoms in an exposure-dependent manner (range of OR for wheeze, chest tightness, attacks of shortness of breath, and attacks of cough: 1.7 [95% CI, 1.02–2.77] to 2.4 [95% CI, 1.29–4.59] in the highest fungal exposure group compared to the lowest and 1.3 [95% CI, 0.77–2.19] to 2.5 [95% CI, 1.30–4.90] in the highest endotoxin exposure group compared to the lowest). The study also demonstrated that workers exposed to high levels of endotoxin and fungi showed much higher risks of building-related wheeze, chest tightness, and shortness of breath compared to workers exposed to high levels of fungi or endotoxin alone, implying a synergistic effect of endotoxin and fungi.
A large United States cross-sectional study using a nationally representative sample of 831 residential homes (2456 residents) found that exposure to *Alternaria alternata* allergen in surface dust was associated with an increased risk for current asthma (physician-diagnosed asthma with asthma symptoms in the past year) [22]. The OR for the second tertile was 1.45 (95% CI, 0.88–2.39) and for the third tertile was 1.73 (95% CI, 1.08–2.77), in models adjusted for age, gender, race, education, smoking, sampling season, dust mite allergens, cockroach allergen, cat and dog allergens, mouse urinary protein, dust weight, and endotoxin, suggesting a linear exposure-response relationship. In models with *A alternata* in dust as a continuous variable and which adjusted for demographics, smoking, and sampling season, the risk for current asthma increased by 31% with each twofold increase in *A alternata* allergen concentration.

A United States study of 190 patients who had asthma and 36 patients who had rhinitis measured forced expiratory volume in 1 second (FEV$_1$) and analyzed dust samples collected from the homes of patients for (1→3)-β-D-glucan (a major carbohydrate constituent of fungal cell walls) and endotoxin [23]. In unadjusted quartile models with mean levels of bed and floor dust endotoxin and (1→3)-β-D-glucan as the exposures and FEV$_1$ percent predicted as the outcome, exposure to endotoxin was associated with a 3% to 6% decrease in FEV$_1$ percent predicted (with a nonlinear relationship). Exposure to increased levels of (1→3)-β-D-glucan had no association with FEV$_1$ percent predicted. A strength of this study was the use of objective pulmonary measurements. A possible limitation was that subjects who did not have asthma or rhinitis were not included for comparison.

In a Turkish case-control study, researchers collected 4-hour airborne fungal samples from living rooms during the winter and compared the levels of culturable fungi in homes with adult patients who had asthma with those in homes of controls [24]. They found that the airborne fungal levels in homes of cases and controls were not different. A limitation of this study was the single measurement per home. Considering that temporal and spatial variations of the airborne fungal concentration are large and that asthma is a chronic disease, their negative finding might have resulted from exposure misclassification.

In a cross-sectional study in Denmark of 522 teachers from 15 schools (8 wet and 7 dry), researchers estimated individual teacher exposures based on dust and air sample measurements from rooms (n = 107) and the number of hours spent in these rooms [25]. Using multivariate logistic regression analyses with three categories of exposure (adjusted for demographics, psychosocial work conditions, and building characteristics), they did not find any significant associations between asthma or objective pulmonary measurements (FEV$_1$, forced vital capacity, and methacholine challenge test results) and exposure to fungi in dust or endotoxin or other microbial agents in dust and air. Although the levels of fungi in dust from rooms in the wet and dry schools were not high, there was approximately a 150-fold
difference between the highest and lowest exposure values in the classrooms. The researchers pointed out that the study was conducted in schools with no history of excessive indoor air problems or health concerns. Therefore, these schools did not represent worst-case scenarios.

**Children**

In a prospective birth cohort study in the Netherlands, researchers collected dust samples from homes of 696 healthy infants at age 3 months and assessed their respiratory health 4 years later [26]. Mothers of all infants had allergy or asthma. Eighteen percent of the infants developed physician-diagnosed asthma. Dust samples were collected from living room floors and the infants’ mattresses and were analyzed for endotoxin, \((1 \rightarrow 3)-\beta\)-D-glucan, and extracellular polysaccharide (carbohydrate in fungal cell walls) of *Aspergillus* and *Penicillium* species (EPS-Pen/Asp). They found that exposure to increasing levels of living room endotoxin and EPS-Pen/Asp during the first 3 months of life had significant protective effects on development of asthma during the first 4 years of life. Using models adjusted for gender, region, parental education, exposure to indoor tobacco smoke, and number of children in the household, the protective effect in the medium exposure group for endotoxin (OR 0.47; 95% CI, 0.26–0.86) was stronger than in the medium exposure group for EPS-Pen/Asp (OR 0.78; 95% CI, 0.40–1.55); and the protective effect in the high exposure group for endotoxin (OR 0.40; 95% CI, 0.21–0.77) was similar in strength to the high exposure group for EPS-Pen/Asp (OR 0.42; 95% CI, 0.18–0.99). The investigators found no associations of exposure to \((1 \rightarrow 3)-\beta\)-D-glucan with asthma development.

A case-control study in Finland investigated home characteristics and levels of various microbial agents, including endotoxin, 3-hydroxy fatty acids (a biomarker of lipopolysaccharide), ergosterol, fungi, and actinomycetes (a large group of gram-positive bacteria), in house dusts of 36 children who had newly diagnosed asthma or who were referred to a hospital because of a history of two or more attacks of wheezing and 36 control children (age range 1 to 7 years old) [27]. Researchers found an increased risk for developing asthma with exposure to higher concentrations of mesophilic actinomycetes, mesophilic and xerophilic fungi, and ergosterol (adjusted OR range 1.08–1.18). In this study, ORs were small and statistical significance was marginal, possibly because of small sample size.

A cross-sectional study performed in rural areas of three countries in Europe collected dust samples from the mattresses of children and analyzed these samples for endotoxin and muramic acid (a sugar in the peptidoglycan layer of bacterial cell walls) [28]. They studied 241 farm and 311 non–farm school children through a questionnaire and a skin test for a mixture of aeroallergens (grass pollen, birch pollen, mugwort pollen, Der p1, cat dander, dog dander, and *Cladosporium herbarum*). In an analysis stratified by sensitization, they found that muramic acid had a protective effect on
wheeze in the past 12 months and on physician-diagnosed asthma in a linear exposure-dependent manner among nonsensitized children. Among the sensitized children, however, no linear exposure-response relationship was found. In this analysis, they adjusted for age, gender, study area, family history of asthma or hay fever, educational level of parents, number of older siblings, living on a farm, and mattress dust endotoxin concentration. Thus the effect of muramic acid was independent of endotoxin and farming environments. This study suggests that the effect of exposure to specific microbial agents on asthma and asthma symptoms in children may be modified by sensitization status.

A cross-sectional study of 1014 primary school children in Sweden analyzed culturable fungi and bacteria, microbial volatile organic compounds (MVOCs), plasticizers, and total fungal and bacterial counts in air samples collected from 23 classrooms in eight schools [29]. Researchers used school-specific mean values of each analyte as an average exposure for all participants in each school. In logistic regression models adjusted for age and gender, they found significant positive associations between exposure to several individual MVOCs and wheeze, nocturnal dyspnea, and physician-diagnosed asthma (OR range 1.03–3.41); total MVOCs and nocturnal dyspnea (OR 5.25; 95% CI, 1.82–15.18) and physician-diagnosed asthma (OR 2.07; 1.09–3.93); and a plasticizer (2,2,4-trimethyl-1,3-pentanediol diisobutyrate) and wheeze, daytime dyspnea, nocturnal dyspnea, and physician-diagnosed asthma (OR range 1.85–5.71). One study limitation was the assumption that measured volatile organic compounds were of microbial origin. Significant but small protective effects were found for total fungal counts on wheeze in the past 12 months (OR 0.98; 95% CI, 0.96–1.00), total bacterial counts on nocturnal dyspnea in the past 12 months (OR 0.92; 95% CI, 0.87–0.98), total culturable bacteria on nocturnal dyspnea (OR 0.92; 95% CI, 0.87–0.98), and total culturable bacteria on physician-diagnosed asthma (OR 0.97; 95% CI, 0.94–1.00). The investigators questioned these protective effects and discussed that exposure misclassification bias may have occurred due to restrictions on opening of windows during the sampling period; however, how this misclassification produced the small protective effects of fungal and bacterial exposure is not clear.

A 1-year study followed 17 children who had asthma and rhinitis and two children who had rhinitis alone who had a positive skin test for one or more fungal allergens (Cladosporium, Alternaria, Penicillium, or Aspergillus) [30]. Over a 1-year period, researchers collected monthly air samples for culturable fungi from the homes of the children. The researchers did not find significant correlations between total or individual airborne culturable fungi and daily asthma score (based on symptoms, daily medication use) and morning or evening peak expiratory flow. Only simple correlations between mold levels and health outcomes were performed, however. Longitudinal data analysis accounting for correlations among
repeated measurements adjusted for demographics and other potential confounding factors may have provided more reliable and complete results.

These studies present evidence that exposures to specific microbial agents in damp indoor environments are associated with development of asthma and asthma-like symptoms in adults. In contrast, studies among infants and young children have found adverse and protective effects. This duality of response in infants and children to microbial exposures has been a topic of much discussion in the literature since the effects of unhygienic conditions in relation to the development of allergic illnesses were first published [31]. A recent editorial expands on the complexities of exposure characteristics and genetic factors that may influence health outcomes [32].

**Intervention studies in relation to asthma and asthma-like symptoms**

Three damp/moldy building remediation health studies with some aspects pertinent to asthma or asthma-like symptoms were reviewed by the IOM; two were among children in Finnish schools [33,34] and one was among office workers [35]. All three studies reported some decrease in respiratory symptoms after remediation. Among the office workers, there was no new asthma after relocation or after return to the remediated building. Prevalences of chest tightness, shortness of breath, cough, and wheeze among office workers were not reduced by 4 months after relocation but were lower 4 years after relocation. Eight newer studies are discussed.

*Workplace intervention studies*

A Danish study of employees of a damp/moldy swimming pool complex (which included an office building), before and after remediation, indicated drops in irritative and nonspecific symptoms, but lower respiratory symptoms were not studied [36]. Remediation included replacement of the roof and damp insulation materials below the roof, replacement of portions of the ceiling that were water damaged or contaminated with mold, cleaning of the inner building surfaces, and cleaning of the ventilation system. Researchers were able to document a significant decline in peak flow variability (20% to 15%) based on 2-week peak flow monitoring results before and 6 months after remediation, indicating intervention effectiveness.

A double-blind multiple crossover study in office workers in three Canadian office buildings investigated the effect of ultraviolet (UV) germicidal lights installed in the heating, ventilation, and air conditioning (HVAC) systems on symptoms [37]. Despite noninclusion of buildings with known outbreaks of building-related illness or which were known to have substantial microbial contamination, researchers found that the use of UV lights lowered the prevalence of cough, chest tightness, and difficulty breathing. This effect was seen most strongly among never-smokers. The UV lights led to a 99%
reduction of microbial contamination on exposed surfaces within the HVAC system but had no effect on airborne microbial concentrations.

School intervention studies

A study of a Swedish school with moisture problems found a decrease in lower respiratory symptoms (including dyspnea and cough) among the staff 7 months after remediation. Remediation consisted of ventilation of the damp concrete slab foundation and replacement of interior walls that had sustained water damage during repair of a prior roof leak. There was no change in lower respiratory symptoms among pupils but there was a decrease in some upper respiratory symptoms [38].

A 3-year follow-up of Finnish teachers in a damp/moldy school with a cluster of eight asthma cases (26%) and a reference school found that before and after remediation wheezing and dyspnea was higher in the damp/moldy school and that the asthma cases were still on similar asthma medication after remediation [39]. Remediation included replacement of mold-contaminated materials and repair of water leaks. The study did find some beneficial effects in regards to no new diagnosis of asthma and significant decreases in conjunctivitis, bronchitis, and sinusitis in the teachers after remediation.

A 5-year follow-up study of Finnish children in a damp/moldy school that underwent remediation found mixed results in terms of improvement in health after remediation [40]. Remediation included an improved rainwater drainage system, improved water barrier on the basement walls, replacement of water-permeable materials with non–water-permeable materials in building locations prone to high moisture loads, improved ventilation in crawl spaces, replacement of damaged materials, and extensive cleaning and disinfection of all surfaces after remediation. There were decreasing trends over time for sinusitis, nocturnal cough, and asthma in all students and in a smaller group of students who participated in all three surveys. There was no clear trend in other respiratory or nonspecific symptoms. Prevalences of symptoms in students who first occupied the school after remediation were lower than in the students who had occupied the school before remediation.

Another Finnish study of elementary students in a damp/moldy school and a reference school found that symptoms were higher in students in the damp/moldy school compared to the reference students before but not during remediation [41]. Researchers surmised that there could have been some over-reporting during the preremediation surveys. Remediation included correction of moisture problems, installation of a mechanical exhaust and supply ventilation system to replace the natural ventilation system, and thorough cleaning after remediation. After remediation, study symptoms prevalence at the two schools were similar (including lower respiratory symptoms of cough, wheeze, and dyspnea) indicating that remediation may have been effective in improving health.
Home intervention studies

A randomized controlled trial in the United States recruited children (2 to 17 years old) who had asthma from a pediatric hospital in Cleveland, Ohio. All children lived in a home with visible mold based on an inspection [42]. Children were randomized to remediation (n = 29) and control groups (n = 33). Home remediation included removal of mold from hard surfaces, elimination of rainwater intrusion, installation of ventilation systems to exhaust water vapor from kitchens and bathrooms, and repair of plumbing leaks. The two groups had a standardized treatment regimen and measures were taken to minimize treatment barriers. There was a significant reduction in symptomatic days per month for the remediation group compared to the control group during the 10th and 12th months of the study. In addition, there were significantly fewer emergency department visits or hospitalizations among children in the remediation group (4%) compared to the control group (33%).

A randomized control trial in South Wales studied 164 houses with dampness/mold, each with at least one occupant who had asthma [43]. Asthmatic subjects (n = 232) ranged in age from 3 to 61 years. Houses were randomly allocated to an intervention group or control group. Intervention consisted of visible mold removal, treatment with fungicide, and installation of a fan in the loft to improve ventilation. Over the 12 months of the study, asthma symptoms and asthma medication use declined in the intervention group, but no difference was found between intervention and control groups in changes in variability of peak flow.

Summary

Based on their review of the literature up to late 2003, the IOM concluded that there was sufficient evidence for associations between exposure to damp indoor environments or mold or other agents in damp indoor environments and asthma-like symptoms, and limited or suggestive evidence for associations with asthma development and dyspnea. They suggested that respiratory effects be studied through additional prospective and intervention studies. Recent epidemiologic studies not included in their report provide additional evidence for an association between damp indoor environments and asthma development and dyspnea. There is some evidence that remediation reduces respiratory health effects, but lower respiratory symptoms may take some time to resolve and dampness-related asthma among occupants may not completely resolve. Exposure to specific microbial agents, such as total fungi, hydrophilic fungi, Cladosporium, Alternaria, and endotoxin, in damp indoor environments is associated with development of asthma and asthma-like symptoms in adults; however, both adverse and protective effects have been identified in studies of infants and children.
References


Indoor Combustion and Asthma
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Combustion indoors produces both gases (eg, nitrogen dioxide, carbon monoxide) and particulate matter that may affect the development or exacerbation of asthma. Sources in the home include both heating devices (eg, fireplaces, woodstoves, kerosene heaters, flued [ie, vented] or nonflued gas heaters) and gas stoves for cooking.

Home heating devices include both those used as the primary heating source and those used as a secondary source. In areas where central heating is the norm (ie, most of the United States), woodstoves, kerosene heaters, or gas space heaters may be used as a secondary source, allowing the family to heat a specific room or to lower the thermostat and reduce the cost of central heating. Some sources may be used only occasionally, such as fireplaces used for ambiance or space heaters used in case of power failure. In other parts of the world such as parts of Europe and China, burning wood or coal within the living space of a home may represent a primary method of heating. These differences in source use (eg, daily versus infrequently, primary versus secondary) lead to considerable variability in exposures.

Gas stoves are another common source of indoor combustion. Exposures to emissions from stoves can also vary considerably depending on stove and household characteristics. Older stoves with continuously burning pilot lights produce significantly more exposure to nitrogen dioxide and particulate matter than stoves with electronic ignition. Other gas appliances, including gas dryers and hot water heaters, may also be sources of exposure to nitrogen dioxide and other pollutants, although exposures tend to be lower from these sources. In the Netherlands, exposure to gas geysers (a type of hot water heater) is common and their effect on respiratory symptoms has been studied [1].

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Supported by grants ES05410 and ES011013 from the National Institute of Environmental Health Sciences.

0889-8561/08/$ - see front matter © 2008 Elsevier Inc. All rights reserved.
doi:10.1016/j.iac.2008.03.011

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Although previous reviews [2] have considered the association of indoor combustion sources with respiratory symptoms in general, this article highlights the recent literature, focusing specifically on exposure to indoor combustion in association with either the development or exacerbation of asthma. Studies of both the incidence and prevalence of asthma in association with indoor combustion sources are included. Severity of asthma will be measured by increases in asthma symptoms (e.g., wheeze, persistent cough, chest tightness and shortness of breath) as well as increases in medication use, physician visits, emergency room visits, and hospitalization. Since asthma is a chronic condition affecting both children and adults, both age groups are included in this review. Heating and cooking devices will be considered separately. Generally, exposure in the home has been investigated. The few studies of children exposed at school [3] are also reviewed.

The following questions are considered in this article: Is indoor combustion associated with asthma development, or with exacerbation of symptoms among asthmatics? Is exposure from heating devices more harmful than exposure from cooking devices? Are specific fuels (e.g., coal), more likely to be associated with risk than others (e.g., wood)? Are children more at risk than adults? Is the association of indoor combustion and asthma confounded by poverty or environmental factors associated with substandard housing or older appliances that burn inefficiently?

**Heating sources**

*Woodstoves*

Wood smoke includes a vast array of constituents forming a complex mix of particles of varying chemical and physical composition, making it difficult to identify any individual harmful constituent [4]. Thus, some have argued that it is best to examine the entire mixture rather than its individual constituents [4]. Factors such as frequency of use, whether the woodburning stove is a primary or secondary heater, ventilation, age, type and condition of the device, and size of home influence concentrations of emissions within the home.

Four studies examined the association of asthma with exposure to a woodstove [5–8]. Of these, only Thorn and colleagues [5] reported a positive association (odds ratio [OR] = 1.7, 95% CI 1.2–2.5). This study compared 174 cases of adult-onset asthma (after age 16 years) with 870 controls randomly selected from a population sample in Sweden. Additional risk factors related to adult-onset asthma in this study were environmental tobacco smoke (OR = 2.4, CI 1.4–4.1), visible mold growth (OR = 2.2, CI 1.4–3.5), and visible dampness with mold growth (OR = 1.8, CI 1.1–3.1). Information about frequency of stove use was not available. No association with asthma was noted for exposure to an open fireplace, tiled stove, or iron stove, although nearly half of the study population reported these exposures.
Three additional studies did not find any association between woodstove exposure and asthma [6–8]. Eisner and colleagues [7] followed 349 adult asthmatics in northern California for 18 months to assess asthma severity. Woodstove exposure was not associated with any of the health indicators that included: asthma severity; general physical health; asthma quality of life; and medical care (emergency department visits or hospital admissions). More frequent use of the woodstove was also not associated with any particular health outcome.

A survey of 10,667 Finnish university students did not find any association of asthma prevalence with exposure to a woodstove for heating in the first six years of life (OR = 0.99, CI 0.65–1.53) [6]. In this study, woodstove heating was associated with living on a farm. Similarly, a survey of 397 school children in Libby, Montana, did not find an association between using a woodstove as the main source of heat, and prevalence of recent wheeze (OR = 1.07, CI 0.47–2.39) [8]. Recent wheeze was analyzed because half of the children with wheeze in the past four weeks did not have an asthma diagnosis. In both Finland and Montana, woodstoves were identified as the main source of heat, reducing the likelihood that negative findings resulted from infrequent use of the stoves.

**Coal stoves**

Coal is composed primarily of carbon, but it also contains sulfur, oxygen and hydrogen. Emissions from coal combustion include a large number of air pollutants such as particulate matter, carbon monoxide, sulfur dioxide, nitrogen oxides, and organic toxics. A handful of studies have examined the association between coal stove use and asthma in children.

In Belfast, Northern Ireland, 2574 children whose names were selected from general practitioners’ lists were studied [9]. Those exposed to glass-fronted solid fuel fires (GFF)—usually burning anthracite—were compared to children in homes with other heating types (primarily oil fired furnaces). Exposure to GFF was associated with all four of these health outcomes: wheeze during the past 12 months (OR = 2.47, CI 1.83–3.30); cough during the past 12 months (OR = 2.20, CI 1.65–2.80); ever used an inhaler (OR = 1.80, CI 1.30–2.30); and diagnosed asthma (OR = 1.81, CI 1.40–2.40). This study also controlled for exposure to environmental tobacco smoke, deprivation score, and crowding. In Munster, Germany, a small number of children (26 out of 3467) who had coal space heaters in their homes [10] were at increased risk for wheeze and asthma; the correlation was made for both boys and girls, although not consistently due to the small sample size.

Use of coal stoves for heating was recently studied with other potential asthma risk factors in China [11]. The International Study of Asthma and Allergies in Children (ISAAC) questionnaire was distributed to all children 6–10 years of age attending 25 randomly selected schools in suburban Beijing. The survey identified 403 children with asthma; 806 controls were
matched for gender, age and class in school. Compared to the use of steam heat, exposure to a coal stove for heating increased the risk of asthma (OR = 1.5, CI 1.1–1.9). Cooking with coal, without a ventilation fan, was associated with an even higher increased risk for asthma (OR = 2.3, CI 1.5–3.5).

A second study investigated household factors and asthma in four Chinese cities (Lanzou, Chongquig, Wuhan, and Gangzhou) [12]. In each city, one urban area with high ambient pollution and one suburban area with low ambient pollution were chosen. Parents of children (n = 7754) attending one school in each area answered a questionnaire. Heating with coal was associated with cough with phlegm (OR = 1.29, CI 1.11–1.50), wheeze (OR = 1.22, CI 1.02–1.45), and asthma, with risks similar to the previous study (OR = 1.52, CI 1.06–2.15). However, cooking with coal was not associated with any health outcome.

Gas heaters

Gas space heaters have nitrogen dioxide (NO₂) emission rates similar to gas stoves. However, because they are used for longer periods of time in living and sleeping areas, there is typically less of a spatial gradient within the home. When they are not vented, use of these heaters can result in NO₂ concentrations four or more times higher than gas stoves used for cooking [13].

A study in Tasmania, Australia investigated exposure to portable or fixed gas space heaters in the first year of life [14]. Data was linked between an infant study of risk factors for SIDS in 1988, and a school study of asthma in 1995. Of 1111 parents who participated in the infant study, 863 also participated in the asthma study. Children exposed to gas heaters in infancy were more likely to develop asthma (RR = 1.95, CI 1.16–3.29) and somewhat more likely to have recent wheeze at age 7 years (RR = 1.63, CI 0.96–2.74), adjusted for smoking in the home and gas cooking. Effects did not differ for children exposed to flued versus nonflued gas heaters. Current exposure to gas heaters at age 7 years was also associated with asthma (RR = 1.33, CI 1.12–1.57) and recent wheeze (RR = 1.41, CI 1.17–1.71). Among infants living in a home with a living room gas heater, those who slept in a room with the door always closed at night had a lower risk of asthma than those who slept with the bedroom door open (RR = 0.26, CI 0.07–0.97). A major strength of this study was the availability of prospective infant data.

The relationship between residential exposures and asthma was also examined in National Health and Nutrition Examination Survey (NHANES) III, a cross sectional study (n = 8257) of a representative sample of children less than six years old in the US [15]. Children in homes where a gas stove or oven was used for heat were more likely to have physician-diagnosed asthma (OR = 1.8, CI 1.02–3.1). Since these stoves are designed for cooking, rather than heating, they are not vented when used as a source of heat.
Fume-emitting heaters

Another study combined different types of heating into two categories: “fume-emitting” and “nonfume-emitting.” In this cross-sectional study of 627 school children (ages 8–11) in Belmont, Australia (a coastal suburb of Sydney), the association between housing characteristics and prevalence of asthma was examined [16]. Questionnaires were completed by parents; airway hyper-responsiveness in the child was measured by histamine challenge; and atopy in the child was measured by skin prick testing to six common allergens. Fume-emitting heating systems included flued gas (4%), nonflued gas (14%), open fire (9%), woodstove (14%), and kerosene (1%); Nonfume-emitting heating systems included central heating (8%), electric heat (47%), and reverse cycle heating (15%). Use of fume-emitting heaters during the first year of the child’s life was associated with airway hyper-responsiveness, (OR = 1.47, CI 1.06–2.03), recent wheeze (OR = 1.44, CI 1.11–1.86), and current asthma (OR = 2.08, CI 1.31–3.31) defined as airway hyper-responsiveness plus recent wheeze. Use of fume-emitting heaters in the first year of life was not associated with asthma when it was alternately defined as a physician diagnosis of asthma (OR = 0.93, 0.74–1.17). In this study, current use of fume-emitting heaters was not associated with any of the asthma-related health outcomes examined. Strengths of this study are: the use of histamine challenge and skin prick testing to obtain objective outcome measures; and adjusting for smoking in the home. In addition, it is unlikely that bias would result in positive associations for exposure in the first year of a child’s life and negative associations with current exposure.

Intervention studies

Two studies have evaluated interventions designed to reduce asthma severity by changing heating systems in children’s homes. In Cornwall, UK, funds from the National Health Service were used to install central heating in the homes of children with asthma to eliminate dampness and increase energy efficiency [17]. Seventy-two children living in 59 homes where the heating system was replaced participated in an evaluation study. There were no control homes. Thirty-three homes previously had coal fires, and 26 homes had other forms of space heating. Central gas furnaces were installed in 37 homes and electric heat in 22. Respiratory symptoms and the number of days lost from school were assessed before and after the intervention. All respiratory symptoms (wheeze, cough, breathlessness) declined after the change in heating system, with the largest decline in cough at night. Days of school lost due to asthma also significantly improved, from a rate of 9.3 per 100 school days to 2.1 per 100 school days. The limitation of this study is the lack of a comparison group, and the possibility that parents were inclined to think their child’s asthma had improved after the change
in heating system and report symptoms differently. The authors attributed the improvement in asthma symptoms to a reduction in dampness in the home (children sleeping in a damp bedroom 61% before, 21% after; children sleeping in a moldy bedroom 43% before, 6% after). However, the intervention also removed coal fires from the homes.

Pilotto and colleagues [3] reported a randomized controlled trial from Adelaide, Australia that studied the effect of replacing nonflued gas heaters in schools. Of 18 schools using nonflued gas heaters, eight were randomized to the intervention group that received flued gas (n = 4) or electric heat (n = 4) depending on cost, and 10 were randomized to the control group with no heater replacement. To maintain blinding of teachers, parents and children, changes to the heating system were disguised as routine maintenance. Asthmatic children, who did not have nonflued gas heaters at home, were eligible for the study (n = 118) and they recorded daily symptoms in a diary for the winter period. Lung function tests (before and after the study period) and skin prick tests were also carried out. Children in the intervention group experienced a reduction in the following symptoms: difficulty breathing during the day (RR = 0.41, CI 0.07–0.98), difficulty breathing at night (RR = 0.32, CI 0.14–0.69), chest tightness during the day (RR = 0.45, CI 0.25–0.81), and asthma attacks during the day (RR = 0.39, CI 0.17–0.93). Results of lung function testing did not differ between the two groups. Nitrogen dioxide levels measured in the intervention classrooms (mean 15.5, SD 6.6) were significantly lower than in control classrooms (mean 47.0, SD 26.8). Because this study was both randomized and blinded, it provides some of the strongest evidence of an association between indoor combustion (and NO 2) and symptoms in asthmatic children.

Cooking appliances

Gas cooking stoves

Gas cooking stoves are an important source of indoor NO 2. However, gas stoves tend to be used for shorter periods of time and are limited to the kitchen, resulting in a strong spatial gradient within the home. A large number of studies have investigated the relationship between gas cooking stoves and asthma prevalence or asthma symptoms. Both adults and children have been studied. Results are inconsistent, but exposure of children appears to be more consistent with risk than exposure of adults. Because gas stoves are used in the kitchen, women are thought to have a much higher exposure on average than men; some studies have considered these gender differences.

Adult exposure

Eisner and colleagues reported two studies of adult exposure to gas cooking and asthma [7,18]. Among 349 adult asthmatics in California, there was no
apparent association of gas cooking with any of the health outcomes: asthma severity; physical health status; asthma quality of life; emergency department visits; or hospital admissions [7]. In NHANES III, 445 adult asthmatics completed pulmonary function testing [18]. There was no association between gas cooking and FEV$_1$, FVC, FEV$_1$/FVC ratio, or FEF$_{25\%-75\%}$, nor was there any association with symptoms (cough, phlegm, dyspnea, or wheeze). However, in a cross sectional study (n = 1159) in East Anglia, UK, gas cooking was positively associated with asthma symptoms and asthma attacks among women: wheeze (OR = 2.07, CI 1.41–3.05); waking with shortness of breath (OR = 2.32, CI 1.24–4.34); asthma attacks (OR = 2.60, CI 1.20–5.65); and use of asthma medication (OR = 2.88, 1.46–5.70) [19]. Women exposed to gas stoves also had lower lung function (% reduction in FEV$_1$ = 3.51 SE 1.2, % FEV$_1$/FVC = 3.07 SE 1.21). No effects were seen in men. The authors argue that women spend more time cooking than men, and short-term “peak” exposures may be more harmful than exposures averaged over longer time periods. Moreover, when all of the European Community Respiratory Health (ECRHS) centers were examined in a subsequent study, the impact of gas stoves was much more variable and inconsistent.

Child exposure

Several studies have examined the impact of gas stove use on asthma in children. A case-control study of Dutch and German children investigated exposure to gas stoves and gas geysers (a type of unvented hot water heater) [1]. Cases (children with asthmatic symptoms) and controls were part of a larger longitudinal study. Parents of 1191 children (age 7–8 years) answered a questionnaire about housing characteristics. Gas cooking with a hood was not associated with asthma status (OR = 0.94, CI 0.60–1.46), but use of an unvented gas geyser significantly increased the risk of asthma symptoms (OR = 3.01, CI 1.21–7.56).

In Victoria, Australia, parents of 148 children (including 53 asthmatics) were interviewed and nitrogen dioxide levels were measured in their homes [20]. Gas stove exposure was associated with asthma diagnosis (OR = 2.23, CI 1.06–4.72) and respiratory symptoms (OR = 2.32, CI 1.04–5.18). The association of gas stoves with respiratory symptoms remained significant (OR = 2.24, CI 1.04–4.82) even after adjusting for measured NO$_2$ concentration. This suggests several possibilities: that other pollutants from gas stoves are responsible for the health effects; that metrics other than average exposure are important; or that unmeasured confounders associated with gas stove use explain the association.

As part of the Yale Childhood Asthma Study, exposures to NO$_2$ and gas appliances were investigated as risk factors for exacerbations of asthma [21]. Children (n = 728) less than 12 years old with active asthma (physician diagnosis and symptom or medication use in the past 12 months) were eligible for the study. At enrollment, research assistants placed Palmes tubes in the home to measure NO$_2$ and recorded the
presence of gas appliances. Mothers reported asthma symptoms in the two months prior to enrollment. To reduce confounding by socioeconomic status and housing characteristics, analyses were stratified by housing type (single family versus multi-family). Asthmatic children living in multi-family housing and exposed to gas stoves experienced increased symptoms of wheeze (OR = 2.27, CI 1.15–4.47), shortness of breath (OR = 2.38, CI 1.12–5.06) and chest tightness (OR = 4.34, CI 1.76–10.69). There was no increase in symptoms associated with exposure to gas dryers, or among children in single-family housing. Exposure to measured NO₂ concentrations confirmed the associations with gas stoves only among children in multi-family housing. The lack of an association of symptoms with exposure in single family homes may be due to the reduced exposure to NO₂ resulting from newer appliances, or it might be due to less personal exposure due to larger homes.

A case control study in Baltimore, MD, specifically looked at exposure to gas stoves among low-income children in the United States [22]. The investigators recruited 150 asthma cases and 150 controls to investigate factors associated with asthma development. All children lived in the inner city and high percentages were from low-income families (88% Medicaid) and were African American (91%). Asthma was not associated with either gas stove exposure or heating systems among these children. Because all subjects were low-income, differences between gas stove users and non-users cannot be attributed simply to poverty or substandard housing.

The effects of ventilation have also been considered to explain the inconsistency in findings about gas stoves. As noted above, Mommers and colleagues [1] specifically analyzed gas stoves with a hood. However, many stoves have hoods that are not vented to the outside, further complicating analysis of the effects of gas cooking. Using birth cohort data from the Netherlands, Willers and colleagues [23] investigated gas cooking, controlling for ventilation. The ventilation variable included an assessment of the effectiveness of an extractor fan, the size of the kitchen, air supply to the kitchen, and use of other ventilation in the kitchen (eg, window fan or ceiling fan). Gas stove use was not statistically associated with asthma in this study (OR = 1.50, CI 0.90-2.49). However, it was strongly correlated with poor ventilation (88% of gas users) and good ventilation was strongly associated with electric stove use (98% of electric users). Thus, information about ventilation did not provide additional information in the analysis of this study.

Some studies have considered gender differences in the effects of gas stove use. In a nationally representative sample (NHANES III) of asthmatic children (8–16 years), Chapman and colleagues [24] compared the effects of gas stove use on lung function in boys and girls. Girls in homes where a gas stove was used for cooking had consistently lower lung function compared to homes with electric stoves. This association was limited to girls who did not use prescription medication for asthma.
The ISAAC questionnaire administered in Munster, Germany (n = 6,996) [10] also noted effects of gas cooking among girls, but not among boys. Gas cooking was positively associated with current wheeze (OR = 1.52, CI 0.93–2.47), but not with asthma (OR = 0.77, CI 0.17–3.46). Some authors [10,19] have suggested that the increased risks for girls in these studies may be because girls are more likely than boys to help their mothers with cooking. However, a Swedish study also reported risks of gas stove exposure specifically in girls, although children in this study were less than 4 years old [25]; at this young age, it is unlikely that girls would be in the kitchen with their mothers more than boys. Children hospitalized for “wheezing bronchitis” (n = 197) were compared to age matched controls (n = 350) selected from population registers in the catchment area of the hospital. Among girls, exposure to a gas stove in the home was associated with wheezy bronchitis (RR = 2.4, CI 1.0–5.9).

Nitrogen dioxide exposure

NO$_2$ is a major pollutant produced by combustion. Some studies have assessed associations between asthma and indoor combustion by directly measuring NO$_2$ concentrations in homes.

The study by Belanger and colleagues [21] (described above) found that exposure to measured NO$_2$ concentrations confirmed associations found with gas stoves. Children exposed to >20 ppb of NO$_2$ in the home had increased days of wheeze (OR = 1.33, 1.05–1.68) and chest tightness (OR = 1.51, CI 1.18–1.91), but only among children in multi-family housing. NO$_2$ concentrations in single family homes (mean [SD] = 10.2 [12.3] ppb) were much lower than in multi-family homes (22.9 [17.0] ppb). In addition, single-family homes were larger (82% had six or more rooms), and personal exposure of children may have been much less than the measured concentration.

Two studies [22,26] specifically looked at exposure to gas stoves and NO$_2$ among low-income children in the United States. In the case control study conducted by Diette and colleagues [22] to investigate factors associated with asthma development, all children lived in the inner city and high percentages were from low-income families (88% Medicaid) and African American (91%). Measured concentrations of NO$_2$ confirmed results described in the previous section suggesting no association between gas stove exposure and asthma development. For NO$_2$, the medians [interquartile ranges] were 21.6[14–34] ppb and 20.9[14–31] ppb in homes of asthmatic children and controls, respectively. Fine particles ≤ 2.5 micrometers in diameter (PM$_{2.5}$) was also measured in the homes; no differences in median concentrations were found in the homes of asthmatics and nonasthmatics (median 28.7 [18–51] ug/m$^3$ and 28.5 [17–50], respectively). Although concentrations did not vary between cases and controls, concentrations of NO$_2$ and PM$_{2.5}$ were high in both groups.

Exposure to indoor combustion was also examined using data from the National Cooperative Inner City Asthma Study [26]. This study examined
environmental factors contributing to increased asthma severity among asthmatic children. Results were reported by measured NO$_2$ concentrations because more than 87% of participants used a gas stove. Children were often exposed to high NO$_2$ concentrations (median = 29.8 ppb), with 15.6% of children exposed in their homes to levels greater than 53 ppb, the US EPA standard for outdoor air quality [27]. Gas stoves were the largest contributor to NO$_2$ concentrations (median = 31.7 ppb and 15.9 ppb for gas stove homes and electric stove homes, respectively). To analyze health outcomes, exposure above the 75 percentile of NO$_2$ was compared to lower exposure and stratified by atopic status. Nonatopic children exposed to more than the 75 percentile of NO$_2$ were at increased risk for more than 4 days of symptoms in a two-week period (OR = 1.75, CI 1.10–2.78) and decreased peak flow (<80% expected) in the winter months (OR = 1.46, 1.07–1.97).

An advantage of these two studies is that all participants were from low-income families, so differences between gas stove users and non-users, or children exposed to different NO$_2$ concentrations, cannot be attributed simply to poverty or substandard housing. A disadvantage of the studies is that so many children were exposed to gas stoves and very high levels of NO$_2$ that the comparison group has nearly as much exposure as the “exposed” group.

In Australia [28], exposure to NO$_2$ was measured both at school and at home for 174 asthmatic children. Relative risks were calculated per 10 ppb NO$_2$. Exposure at school was associated with difficulty breathing during the day (RR = 1.09, CI 1.03–1.15), and at night (RR = 1.11, CI 1.05–1.18); chest tightness at night (RR = 1.12, CI 1.07–1.17); and difficulty breathing after exercise (RR = 1.04, CI 1.01–1.09). Exposure at home was associated with difficulty breathing at night (RR = 1.03, CI 1.01–1.05) and asthma attacks at night (RR = 1.04, CI 1.00–1.07). Home exposure was also associated with decreased lung function (FEV$_1$ = −0.39% predicted per 10 ppb NO$_2$, CI −0.76 to −0.02).

In Japan [29], 842 school children participated in a study that measured NO$_2$ concentrations in their homes and followed the children over three years to assess asthma, bronchitis and wheeze. The use of unvented heaters in the home was associated with higher NO$_2$ concentrations, mean = 34.4 ppb versus mean = 18.4 ppb for homes with vented heaters. However, use of unvented heaters alone was not associated with any of the health outcomes. Exposure to a 10 ppb increase in NO$_2$ was associated with asthma (OR = 1.63, CI 1.06–2.54), bronchitis (OR = 1.42 CI 1.06–1.90) and wheeze (OR = 1.90 CI 1.30–2.83) among girls. Exposure to NO$_2$ was not associated with any health outcome among boys.

**Discussion**

This article did not find any studies that addressed the question of an association between indoor combustion and asthma incidence. To examine...
this question would require a cohort followed from birth. However, several studies considered increased asthma prevalence in association with combustion sources. Eight studies reported positive associations for asthma prevalence among children [9,11,12,14–16,25,29]; two studies reported negative findings [22,23]. Among adults, there was one positive [5] and one negative [6] association. A larger number of studies investigated increased symptoms, usually wheeze, or decreased lung function. Nine studies reported increased symptoms among children [1,3,9,12,16,17,20,21,28] and an additional four studies reported increased symptoms only in girls [10,24,25,29]. Two studies failed to find any association of asthma symptoms in children with combustion sources [8,23]. Among adults, indoor combustion was not associated with increased symptoms in three studies [6,7] and positively associated in one study, only with women [19].

Children appeared to be more susceptible to exposure to indoor combustion than adults; however, it is difficult to assess differences in susceptibility by age. Most studies specifically recruited children and only a limited number of studies of adult exposure was available. In three studies of adults exposed to woodstoves, only one was positive; and in three studies of adults exposed to gas cooking stoves, only one study had positive results, and only among women. Several studies investigating exposure to gas cooking stoves reported exposure associated with asthma in females, but not in males. This association could be explained among adult women, because women do more cooking in most families than men. However, this association was also reported among girls (even girls less than four years old). Differences between boys and girls may be related to exposure, or may indicate gender differences in susceptibility, for example hormonal differences.

In general, exposure from indoor combustion for heating was more consistently associated with risk than exposure from cooking. This may reflect the higher exposure from heating devices that are used for many hours per day, rather than the shorter duration of exposure associated with cooking. Nonflued heating devices were more often associated with asthma prevalence or asthma symptoms than devices with flues. In particular, woodstoves that are always vented produced less risk. Removal of nonflued gas heaters in schools decreased symptoms in asthmatic children, even though some schools replaced these devices with flued gas heaters. Exposure from nonflued devices probably exceeds the exposure from flued devices, which might explain these findings.

It appears that exposure to coal poses a special risk. All studies that reviewed burning coal in the home indicated increased asthma prevalence, and the three studies designed to measure increases in symptoms (e.g., wheeze, phlegm, inhaler use) also noted increased symptoms in asthmatic children. Results were much less consistent for wood, where only one of the four studies indicated a positive association with increased asthma symptoms among adults. Nonflued gas heaters also posed a significant risk, and a randomized
trial provides strong evidence that removing these heaters reduced asthma symptoms in children.

Gas stove use is particularly common in central cities; in the United States, inner cities are associated with high rates of poverty and substandard housing. In rural areas, the use of secondary heating devices (kerosene heaters, unvented gas) may be a means to reduce heating costs among low-income families. Thus, it is possible that gas stoves and portable heating devices are markers for poverty and substandard housing, and this confounds any association with asthma. Two studies specifically analyzed children from low-income families living in inner city neighborhoods. Both studies measured exposure to nitrogen dioxide (one also measured PM$_{2.5}$) and both documented very high exposures (exceeding the US Environmental Protection Agency [EPA] level for outdoor exposure in some cases). However, these studies found limited association with asthma (one found no association; in the other, associations were limited to subgroups). A limitation of these studies is that measured pollutant concentrations indicate there were no truly unexposed controls; even homes without gas stoves had high measured concentrations of NO$_2$. Many of these homes were multifamily and children were probably exposed to pollutants from devices in the building, if not in their own apartments. An intervention study in the UK indicated a reduction in symptoms for children when sources in the home were removed and housing conditions improved.

Overall, it appears that exposure to indoor combustion sources may increase the risk of asthma or asthma severity, particularly in children. Characteristics of the device (eg, frequency and intensity of use, type and age of appliance) and of the home (eg, size, ventilation) result in considerable variability in exposures, which may account for some of the inconsistent findings between studies.

References


Passive Smoking and Adult Asthma

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Asthma is a common chronic health condition, affecting 5% of the United States adult population [1]. In most developed countries, the prevalence of asthma and its severity continues to increase. Understanding the factors contributing to asthma morbidity and mortality has important clinical and public health implications.

Passive tobacco smoking results in exposure to a complex mixture of more than 4,000 chemical compounds, including known carcinogens [2]. Secondhand smoke (SHS) also contains potent respiratory irritants, such as sulfur dioxide, ammonia, formaldehyde, and acrolein. These chemicals irritate the upper and lower respiratory tract (Table 1) and may induce asthma through irritant or sensitizing mechanisms [3]. Because persons with established asthma have chronic airway disease, they may also be susceptible to adverse health effects from SHS exposure. This article evaluates the evidence that SHS exposure is a risk factor for new-onset asthma among adults and exacerbates pre-existing adult asthma, resulting in greater symptom burden and morbidity.

Prevalence of secondhand smoke exposure

In the United States, there has been significant progress in reducing passive smoke exposure. During the period from 1988 to 2002, SHS exposure, as measured by serum cotinine, declined by 70% [4]. Nonetheless, nearly half of all Americans continue to have evidence of recent SHS exposure.

Although they might be expected to avoid SHS, many United States adults with asthma actually experience significant exposure. In a cohort of adults with asthma living in Northern California, 29% reported regular SHS exposure [5]. Among adult health maintenance organization (HMO)
members with asthma, 38% indicated regular exposure [6]. A population-based study from Canada found that 42% of nonsmoking children and adults with asthma reported SHS exposure during the previous 24 hours, compared with 32% of the general population [7]. In the author’s study, using direct measurement of SHS exposure among adults with asthma, an even higher prevalence of exposure was found, ranging from 60% to 83% depending on the time frame and methodology [8]. In sum, it seems clear that adults with asthma continue to experience significant passive smoking exposure.

Secondhand smoke exposure and asthma induction in adults

Extensive data support a causal association between SHS exposure and induction of asthma in children [3]. In a recent meta-analysis of 85 studies conducted by the California Environmental Protection Agency (EPA), passive smoking was associated with an increase in childhood asthma incidence of between 21% and 37% [2]. The literature was deemed to be sufficient to infer a causal relationship between passive smoking and childhood asthma induction. Until recently, however, the relationship between SHS exposure and adult-onset asthma has received less attention [9]. Fig. 1 shows a conceptual model of how SHS exposure may cause adult-onset asthma.

Recent epidemiologic studies have evaluated the impact of SHS exposure on new-onset adult asthma. The Swiss Study on Air Pollution and Lung Diseases in Adults (SAPALDIA) focused on a random sample of adult never-smokers aged 18 to 60 years residing in Switzerland [10]. In a cross-sectional analysis, investigators observed an association between self-reported SHS exposure during the previous 12 months and a greater risk of self-reported physician diagnosis of asthma (odds ratio or OR 1.39; 95% confidence interval or CI 1.04–1.86). Statistically controlling for age,

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gender, atopy, education, maternal and paternal smoking during childhood, and parental asthma history had no appreciable impact on this relationship. Furthermore, the investigators observed statistically significant exposure-response trends for hours per day of SHS exposure, number of smokers, and years of exposure.

A case-controlled study from semi-rural Sweden evaluated SHS exposure as a risk factor for asthma [11]. Asthma diagnosis was confirmed by a study lung specialist. SHS exposure at both home and work was assessed by written questionnaire, which was defined as exposure for at least 3 years before the age at asthma diagnosis (or comparable age for controls). Using this definition, workplace SHS exposure was associated with an increased risk of asthma (OR 1.5; 95% CI 0.8–2.5), but the confidence interval did not exclude no association. Exposure to SHS at home was not associated with the risk of asthma (OR 0.9; 95% CI 0.5–1.5).

A population-based cross-sectional study aimed to elucidate environmental risk factors for asthma and allergic rhinitis among Swedish dairy farmers [12]. By postal questionnaire, asthma was defined as self-reported episodic respiratory symptoms, such as wheezing and dyspnea. SHS exposure was assessed for the current period (home and work) and during childhood. In this study, no measure of SHS exposure, past or present, was associated with the risk of asthma.

In a previous article, the author examined cross-sectional data from 47,721 adult never-smoking Northern California Kaiser Permanente members who underwent multiphasic health check-ups between 1979 and 1985 [13]. Using a written questionnaire, current SHS exposure was ascertained.
for several locations: home, other small spaces (eg, office or car), and large indoor spaces (eg, restaurant). In each location, the survey assessed average duration of exposure. In both men and women, any SHS exposure was associated with a greater risk of self-reported physician-diagnosed asthma (OR 1.22; 95% CI 1.11–1.34), controlling for socioeconomic and demographic covariates. For weekly exposure duration, there was evidence of an exposure-response relation among women but not men.

A population-based study of 8,008 adult never-smokers from Sweden examined the impact of childhood SHS exposure on current self-reported physician-diagnosed asthma during adulthood [14]. The prevalence of adult asthma was more common among subjects who indicated childhood SHS exposure (7.6%), compared with unexposed persons (5.8%) (P = .035). Current self-reported “breathing difficulties from cigarette smoke” were also more common among subjects who indicated a history of childhood SHS exposure. In further analysis, the investigators stratified by family history of asthma. Although there was no clear impact of SHS among subjects without a family history of asthma, SHS exposure was associated with a greater risk of asthma among those with a positive family history (OR 1.82; 95% CI 1.28–2.58). These results could be consistent with higher rates of smoking cessation by asthmatic parents, reducing exposure of their children with asthma.

The European Community Respiratory Health Survey investigators examined the respiratory health impacts of SHS exposure among 7,882 adult never-smokers aged 20 to 48 years [15]. Compared with no SHS exposure, any SHS exposure at home or work was not clearly associated with a greater risk of self-reported current asthma (OR 1.15; 95% CI 0.84–1.58). When each source of exposure was examined individually, workplace exposure was related to a higher risk of asthma (OR 1.90; 95% CI 1.25–2.88). There was no clear impact of home exposure (OR 1.14; 95% CI 0.68–1.90). These apparently discrepant results could be explained by the method of SHS exposure measurement. Home exposure was defined as living with at least one smoker, whereas workplace exposure ascertained regular smoking in the room where they worked. Because residence with a smoker may not always reflect domestic SHS exposure, use of this exposure measure could attenuate the effect estimate for home SHS exposure [16].

The investigators also found a similar pattern of results for several asthma-like symptoms, including wheeze, nocturnal chest tightness, and dyspnea. In these instances, workplace SHS exposure was related to a greater risk of respiratory symptoms, whereas home exposure had no apparent impact. Furthermore, both home and workplace SHS exposure were associated with greater bronchial hyper-responsiveness assessed by methacholine challenge. Because bronchial hyper-responsiveness is a cardinal feature of asthma, this result adds additional support to the observed link between SHS exposure and self-reported asthma.

A Swedish population-based case-controlled study examined the impact of SHS exposure on adult-onset asthma (age >16 years) [17]. The
investigators ascertained home exposure only, during or previous to the year of asthma diagnosis (and at a randomly selected time for control subjects). In this study, SHS exposure was associated with a greater risk of adult-onset asthma (OR 2.4; 95% CI 1.4–4.1). This increased risk was observed only among never-smokers and not among current or ex-smokers. When the results were stratified by sex, the association was stronger for males (OR 4.8; 95% CI 2–11.6) than for females (OR 1.5; 95% CI 0.8–3.1).

Hu and colleagues [18] evaluated a cohort of 1,469 seventh grade students 7 years after a school-based smoking prevention program in southern California. At baseline, SHS exposure status was determined by parental reports of personal smoking. During young adulthood (7 years later), self-reported physician diagnosed asthma was ascertained by written questionnaire. Exposure to parental SHS at baseline was associated with an increased risk of subsequent asthma. Compared with no maternal smoking or light smoking at baseline (less than one-half pack per day), heavier maternal smoking was associated with an increased risk of self-reported asthma in young adulthood (OR 1.8; 95% CI 1.1–3.0). Similarly, heavy paternal smoking was related to a greater risk of asthma (OR 1.6; 95% CI 1.1–2.4). In addition, they observed an exposure-response relationship between number of parents smoking at baseline and the risk of asthma 7 years later.

A longitudinal cohort study of 3,914 adult nonsmoking Seventh-Day Adventists living in California evaluated the relationship between SHS exposure and the incidence of self-reported physician diagnosed asthma during a 15-year period [19,20]. The investigators reported the 10-year [19] and 15-year cohort follow-up [20]. Duration of working with a smoker was associated with an increased risk of developing asthma (OR 1.5 per 10-year increment; 95% CI 1.2–1.8). At the 15-year follow-up, duration of working with a smoker was associated with an increased risk of incident asthma for women only (OR 1.21; 95% CI 1.04–1.39). In both analyses, there was no reported relationship between duration of residence with a smoker and risk of asthma.

A recent population-based cross-sectional study from India examined the impact of home SHS exposure on self-reported asthma diagnosis on 62,109 never-smoking adults [21]. SHS exposure was associated with asthma after adjusting for age, gender, usual residence, exposure to biomass fuels, and atopy (OR 1.22; 95% CI 1.08–1.38). Respondents who reported both childhood SHS exposure and home exposure during adulthood had highest risk of having asthma (OR 1.69; 95% CI 1.38–2.07).

A seminal population-based case-controlled study examined the relation between SHS exposure and new onset adult asthma among 239 asthma subjects and a 487 matched controls in Finland [22]. Lifetime passive smoke exposure was ascertained by questionnaire. Logistic regression analysis was used to control for age, gender, parental atopy or asthma, education, mold exposure, pets in the home, and other occupational exposures. The
incidence of adult-onset asthma was significantly associated with total SHS exposure (combined home and workplace) during the preceding 12 months (OR 1.97; 95% CI 1.19–3.25) with evidence of an exposure response relationship (OR 1.33 per 10 cigarettes per day; 95% CI 1.02–1.75). After controlling for exposure at home, any exposure to SHS in the workplace was also associated with an increased risk of asthma (OR 2.16; 95% CI 1.26–3.72). There was also a substantive risk of asthma related to home SHS exposure (OR 4.77; 95% CI 1.29–17.7). When passive smoking was analyzed as cumulative lifetime exposure, the risk of asthma was also increased, especially from workplace and combined exposures. This study is important because it had excellent lifetime exposure estimation, was population based, and clearly ascertained adult onset asthma cases.

There is no gold standard for defining asthma in epidemiologic research. Although self-reported asthma is commonly used in survey research, this definition may not detect all persons with asthma [23,24]. Respondents’ reports of respiratory symptoms, especially wheezing, may have a greater sensitivity for identifying adults with asthma [24]. Wheezing, in particular, correlates with the criterion of bronchial hyper-responsiveness (see Fig. 1) [25]. Earlier epidemiologic studies supported the relationship between SHS exposure and wheezing among adults [10,26–29]. Several more recent studies further support this relationship.

In the SAPALDIA study, SHS exposure during the previous 12 months was associated with a greater risk of wheezing (OR 1.94; 95% CI 1.39–2.70), dyspnea on exertion (OR 1.45; 95% CI 1.2–1.79), and chronic bronchitis symptoms of cough or phlegm production (OR 1.65; 95% CI 1.17–2.16) [10]. As in the analysis focusing on asthma, controlling for demographic and socioeconomic covariates had minimal effect. For these symptom endpoints, investigators observed exposure-response trends for hours per day of exposure, number of smokers, and years of exposure.

Using a case-crossover design, the author and colleagues studied the effects of California State Assembly Bill 13, which prohibited tobacco smoking in bars and taverns, on the respiratory health of bartenders [30]. Based on a random sample of all bars and taverns in San Francisco, the investigators interviewed and performed spirometry on 53 bartenders before and after the smoking ban. After prohibition of smoking, self-reported workplace SHS exposure sharply declined from a median of 28 to 2 hours per week. Of the 53 bartenders, 39 (74%) reported at least one respiratory symptom at baseline (including cough, dyspnea, and wheezing), while only 17 (32%) were still symptomatic at follow-up. Of the 39 bartenders reporting baseline symptoms, 23 subjects (59%) no longer indicated any respiratory symptoms after prohibition of smoking ($P < .001$). In particular, 70% of the 17 bartenders reporting baseline wheezing noted resolution after workplace smoking prohibition. In conditional logistic regression analysis, a 5-hour reduction of workplace SHS exposure was associated with a lower risk of respiratory symptoms at follow-up (OR 0.7; 95% CI 0.5–0.9), after
controlling for upper respiratory infections and reduced personal cigarette smoking. After prohibition of workplace smoking, the investigators also observed improvement in mean forced vital capacity (FVC) (0.189 L; 95% CI 0.082–0.296) and mean forced expiratory volume in the first second of expiration (FEV$_1$) (0.039; 95% CI −0.030 to 0.107). Complete cessation of workplace SHS exposure was associated with an even greater pulmonary function improvement.

More recently, Menzies and colleagues [31] reported the effects of a national smoking ban on bar workers in Scotland. Using a design similar to the author’s earlier study [30], these investigators documented markedly reduced SHS exposure after the smoking ban, based on both self-reported exposure and a biomarker of SHS exposure (serum cotinine). After the smoke-free legislation went into effect, bar workers experienced sustained reduction of sensory irritation symptoms and respiratory symptoms as well as improved pulmonary function.

The study by Menzies and colleagues [31] confirms and amplifies previous research demonstrating reduced SHS exposure and decreased respiratory symptoms among restaurant and bar workers after smoke-free workplace mandates in the United States [30,32,33], Ireland [34–37], Norway [38], and New Zealand [39]. Taken together, there is compelling scientific evidence that smoke-free workplace legislation is rapidly effective in preventing asthma-like respiratory symptoms.

The study by Menzies and colleagues [31] also provided valuable new information about bar workers with asthma. After the Scottish smoking ban went into effect, bar workers with asthma experienced an even larger improvement in pulmonary function than those without asthma. Moreover, the asthmatics had evidence of reduced airway inflammation (exhaled nitric oxide) and improved asthma-specific quality of life. Consequently, it appears that the benefits of smoke-free workplace legislation are even greater for persons with asthma.

A population-based longitudinal cohort study from the United Kingdom followed children aged 6 to 8 years into adolescence (age 14–16 years) to examine factors associated with the development of respiratory symptoms [40]. In adolescence, SHS exposure was cross-sectionally associated with current wheeze (OR 1.48; 95% CI 1.17–1.88). Maternal smoking was related to a greater risk of parent-reported physician-diagnosed asthma (OR 1.50; 95% CI 1.14–1.98). There was no apparent impact of paternal smoking on current asthma. Among previously asymptomatic persons, paternal smoking was associated with new-onset wheeze during prospective follow-up (OR 1.55; 95% CI 1.03–2.32). Maternal smoking, however, was not associated with new-onset wheeze. New-onset asthma was not examined.

Another population-based United Kingdom cohort study followed 18,559 children born during a single week in March 1958 through age 33 (31% complete follow-up) [41]. The study examined the association between household SHS exposure and the future incidence of wheezing.
At both age 7 and 33 years, maternal smoking during pregnancy was associated with an increased risk of incident wheezing illness (OR 1.72; 95% CI 1.11–2.67 and OR 1.71; 95% CI 0.97–3, respectively). At age 33, maternal smoking at subject age 16 was associated with an increased incidence of wheezing (OR 1.19; 95% CI 0.86–1.65). SHS exposure both during pregnancy and age 16 was related to a greater risk of incident wheezing (OR 1.4; 95% CI 1.08–1.82). This study is limited by the low follow-up at age 33, which could have biased the results if SHS exposure was related to the probability of study participation.

A population-based study of 2,195 Italian women examined the impact of exposure to self-reported history of home and workplace SHS exposure (ever- versus never-exposed) [42]. SHS exposure from both a husband and at work were significant risk factors for current dyspnea (OR 1.61; 95% CI 1.20–2.16), recent wheeze (OR 1.71; 95% CI 1.04–2.82), recent attacks of shortness of breath with wheeze (OR 1.85; 95% CI 1.05–3.26), and self-reported physician diagnosis of asthma diagnosis or respiratory symptoms (OR 1.50; 95% CI 1.09–2.08). The impact of SHS exposure on asthma diagnosis alone was not examined.

Measurement of SHS exposure by self-report is potentially subject to bias, which limits many of the studies reviewed. The impact of exposure misclassification may be particularly problematic in cross-sectional studies. For example, adults with asthma might be more likely to remember and report SHS exposure, whereas asymptomatic persons might underreport SHS exposure. This bias would inflate the estimated risk associated with SHS exposure. In many studies examined, systematic misclassification of SHS exposure cannot be excluded. The prospective data, however, should be less affected by this potential bias. Moreover, studies that employed direct markers of SHS exposure, such as cotinine or personal nicotine exposure, would be free from this reporting bias.

The consistency of study findings helps to support a causal relationship between SHS exposure and adult asthma induction. In samples drawn from different populations, ranging from clinical to population-based samples, and different countries around the world, investigators have observed the association between SHS exposure and new-onset asthma. The relationship between SHS exposure and asthma has been observed in a variety of study designs, including cross-sectional, case-controlled, and cohort studies. Exposure in different environments, such as home and work, has also been linked with asthma. The consistency of findings linking SHS exposure with different related respiratory health outcomes, including new-onset asthma and wheezing, supports a deleterious causal effect of SHS exposure on adult asthma.

Because SHS contains potent respiratory irritants, exposure may adversely affect bronchial smooth muscle tone and airway inflammation [3]. Studies linking SHS exposure with a decrement in pulmonary function support the biologic plausibility of SHS-related asthma onset. Taken
together, studies of adults support a small but significant deleterious effect of SHS on pulmonary function [26–28,30,43–54].

The studies reviewed also demonstrate coherence in the association between SHS exposure and asthma morbidity. SHS exposure has been associated with new-onset asthma, whether defined as self-reported physician diagnosed asthma or a clinical asthma diagnosis. Furthermore, SHS exposure is associated with related health outcomes, including other chronic airway diseases and respiratory symptoms, such as wheezing, cough, and dyspnea. The coherence of these findings among diverse respiratory outcomes supports a causal association.

**Secondhand smoke exposure and exacerbation of pre-existing adult asthma**

Because adults with asthma have chronic airway inflammation, they may be particularly susceptible to the effects of SHS exposure. Both the California EPA and United States EPA have affirmed a causal connection between passive smoke exposure and exacerbation of pre-existing asthma among children [2]. Adults with asthma commonly report SHS exposure as a trigger for asthma exacerbation [55,56]. However, the impact of SHS exposure on adults with asthma has received less research than in children.

Recent epidemiologic studies support a link between SHS exposure and adult asthma exacerbation. In a cross-sectional study, investigators examined the impact of self-reported SHS exposure on 200 never-smoking adults with asthma attending a university-based chest clinic in India [57]. Compared with unexposed patients, adult asthmatics reporting SHS exposure indicated greater reliance on daily bronchodilators (66% versus 56%, \( P < .01 \)) and intermittent corticosteroid use (56% versus 42%, \( P < .01 \)). Although there was no relationship with hospitalization, SHS-exposed subjects had a higher mean number of emergency department visits for asthma during the previous year (0.82 visits per person versus 0.6 visits per person, \( P < .01 \)) and more work absence (3.6 weeks per person versus 3 weeks per person, \( P < .01 \)). SHS exposure was also associated with worse pulmonary function, including lower FEV\(_1\) (68.7% versus 80.8% of predicted), FEV\(_1\)/FVC (63.5% versus 78.4%), and forced expiratory flow (FEF\(_{25\%–75\%}\) (54.3% versus 75.7%).

In the Swedish component of the European Community Respiratory Health Survey, Blanc and colleagues [58] examined the cross-sectional impact of self-reported workplace SHS exposure among 2,065 adults (aged 20–44 years). Regular workplace SHS exposure was associated with a greater risk of respiratory-related work disability (prevalence ratio 1.8; 95% CI 1.1–3.1), defined as self-reported change in job or leaving work because of affected breathing. Moreover, workplace SHS exposure was related to a greater risk of work-associated symptomatic asthma, defined as self-reported asthma, airway hyper-responsiveness, and work-related chest tightness or wheezing (prevalence ratio 1.7; 95% CI 0.9–3.3). Because this study
focused on workplace factors, home and other sources of SHS exposure were not examined.

In a prospective panel study of 164 adult nonsmokers with asthma, Ostro and colleagues [59] examined the impact of SHS exposure on asthma status during a 3-month period. Subjects completed daily diaries, including SHS exposure (home and work) and respiratory symptoms. During longitudinal follow-up, SHS exposure was associated with subsequent greater risks of cough (1.21; 95% CI 1.01–1.46), dyspnea (OR 1.85; 95% CI 1.57–2.18), nocturnal asthma symptoms (OR 1.24; 95% CI 1–1.53), and restricted activity (OR 2.08; 95% CI 1.63–2.64). In this longitudinal panel study, the close temporal link between SHS exposure and outcome supports a causal relationship between exposure and asthma exacerbation.

In an analysis of 43,732 adults completing the Health Promotion and Disease Prevention supplement of the 1991 National Health Interview Survey, the cross-sectional association between self-reported SHS exposure at home or work and the risk of “chronic respiratory disease exacerbation” was examined [60]. This study outcome was defined as activity limitation or a physician visit because of a chronic respiratory disease: asthma, chronic bronchitis, emphysema, or chronic sinusitis. Among never-smokers, SHS exposure was associated with an increased risk of chronic respiratory disease exacerbation (OR 1.44; 95% CI 1.07–1.95). Although the population-based sampling and careful control of confounding are study strengths, the relationship between SHS exposure and asthma alone cannot be clearly elucidated from the published study.

Using data from the Third National Health and Nutrition Examination Survey, the author examined the relationship between serum cotinine and pulmonary function among 440 nonsmoking adults with asthma (corresponding to a population of 4.9 million asthmatics) [53]. There was no apparent impact of SHS exposure, as measured by serum cotinine level and pulmonary function among men. In the female stratum, higher levels of SHS exposure were associated with greater impairment of FEV\textsubscript{1}, FVC, and FEV\textsubscript{1}/FVC ratio. In particular, the highest cotinine tertile was related to a mean FEV\textsubscript{1} decrement of $-261$ mL (95% CI $-492$ to $-30$). The impact of SHS exposure appeared to be greater among adults with asthma when compared with nonsmoking members of the general population.

The SAPALDIA study focused on a random sample of adult never-smokers aged 18 to 60 years residing in Switzerland. A report from the SAPALDIA investigators found similar effects of self-reported SHS exposure on pulmonary function among 3,534 never-smoking adults with asthma [61]. SHS exposure at work was related to a substantive decrement of FEV\textsubscript{1} ($-4.8\%$), FVC ($-1.7\%$), and forced expiratory flows at mid-lung volumes (FEF\textsubscript{25%–75%}, $-12.4\%$). The impact of SHS exposure on FEV\textsubscript{1} and FEF\textsubscript{25%–75%} was greater among women than men ($-8.7\%$ versus 0.5% and $-20.8\%$ versus $-1.4\%$, respectively). There was evidence of linear exposure-response trend for daily exposure duration and numbers of years of exposure.
In a cross-sectional study, Jindal and colleagues [62] recruited 50 women with asthma from a university hospital chest clinic in India. SHS exposure at home and work was assessed by questionnaire. Compared with women who indicated no SHS exposure, subjects indicating any SHS exposure had similar FEV1 (78% predicted versus 79%) and FEV1/FVC ratio (94% versus 86%) (P = not significant in both cases). The SHS-exposed women had greater bronchial hyperresponsiveness, as indicated by lower PD20 (median 1.70 versus 6.1 units; P < .01). SHS exposure was also associated with greater asthma medication use. The proportion who indicated “continuous” bronchodilator use was higher among exposed women (39% versus 26%; P < .05), although the precise definition of this term was not provided. Taken together with the European Community Respiratory Health Survey results described earlier, SHS exposure is related to greater bronchial hyperresponsiveness among adults with asthma.

A cohort study of 619 adult HMO members with asthma evaluated the association between SHS exposure and health outcomes [6]. The prevalence of self-reported regular SHS exposure was 38% and a small proportion of subjects (11%) indicated current personal cigarette smoking. In cross-sectional analysis of baseline data, regular SHS exposure was associated with worse asthma-specific quality of life and generic health status (SF-36 physical functioning and general health domains). During longitudinal follow-up, SHS exposure was associated with a greater incidence of hospital-based episodes of asthma care (28 events versus 10 events per 100 person-years). After controlling for sociodemographic covariates, SHS exposure was with a greater risk of hospital-based care (risk ratio 2.34; 95% CI 1.8–3.1).

To study the impact of SHS exposure on adults with asthma, the author and colleagues used data from an ongoing prospective cohort study of adults with asthma recruited from a random sample of allergy, pulmonary, and family practice physicians practicing in Northern California [16]. Of the overall cohort, the investigators recruited 50 subjects to wear a personal nicotine badge monitor for 1 week. At the conclusion of the monitoring period, respiratory symptoms and medication use were ascertained. Compared with subjects with no measurable nicotine levels for the past 7 days, lower level (0 μg/m3–0.05 μg/m3) and higher level exposure (>0.05 μg/m3) were associated with a greater risk of respiratory symptoms at follow-up (OR 1.9; 95% CI 0.4–8.8 and OR 6.8; 95% CI 1.4–32.3). Lower- and higher-level SHS exposures were also related to an increased risk of extra bronchodilator use after exposure (OR 2.2 and 8.1). For both outcomes, there was evidence of a linear exposure-response relationship.

In the larger prospective cohort study of 349 adults with asthma, the author and colleagues examined the impact of self-reported SHS exposure on subsequent health outcomes [63]. SHS exposure at baseline interview was associated with impaired health status at longitudinal follow-up. Compared with respondents with no baseline self-reported exposure to SHS,
higher level exposure (> 7 hours per week) was associated with worse severity of asthma scores at follow-up, controlling for baseline asthma severity, age, sex, race, income, and educational attainment (mean score increment 1.5 points; 95% CI 0.4–2.6). Higher-level baseline exposure to SHS was also related to poorer physical health status (mean decrement −4.9 points; 95% CI −8.4 to −1.3) and asthma specific quality of life (mean increase 4.4 points; 95% CI −0.2 to 9) at longitudinal follow up. Higher-level baseline SHS exposure was associated with a greater risk of emergency department visits (OR 3.4; 95% CI 1.1–10.3) and hospital admissions for asthma at prospective follow up (OR 12.2; 95% CI 1.5–102). Taken together with the direct exposure measurement results from this cohort, these studies support the adverse impact of passive smoking on adult asthma status.

In another prospective cohort study of adult nonsmokers recently admitted to hospital for asthma, the impact of SHS exposure on asthma health outcomes was examined [8]. Recent SHS exposure during the previous 7 days was directly measured using a personal nicotine badge (n = 189) and exposure during the previous 3 months was estimated using hair nicotine and cotinine levels (n = 138). Asthma severity and health status were ascertained during telephone interviews, and subsequent admission to hospital for asthma was determined from computerized use databases. The highest level of recent SHS exposure, as measured by the personal nicotine badge, was related to greater asthma severity (mean score increment for highest tertile of nicotine level 1.56 points; 95% CI 0.18–2.95), controlling for sociodemographic covariates and previous smoking history. Moreover, the second and third tertiles of hair nicotine exposure during the previous month were associated with a greater baseline prospective risk of hospital admission for asthma (hazard ratio or HR 3.73; 95% CI 1.04–13.30 and HR 3.61; 95% CI 1–12.9, respectively).

A prospective cohort study from Canada followed children and adults with asthma for the development of acute exacerbation [64]. The main goal was to evaluate the impact of viral upper respiratory infections on the risk of asthma exacerbation. More than half of the subjects were aged 13 years or greater (58%), ranging up to age 55 years. Within the cohort, a nested case-controlled study was performed, with cases of acute asthma exacerbation compared with controls without exacerbation. Cases with asthma exacerbation were defined by increasing asthma symptoms refractory to usual medications for more than 48 hours or urgent health care use for asthma: hospitalization, emergency department visit, or urgent physician visit. Cases (with acute asthma exacerbation) were more likely to have indicated SHS exposure during the previous year (39%) than controls without exacerbation (17%) (P < .03) (Tarlo SM, personal communication, 2002) [64]. Although the investigators ascertained exposures to colds, dust, and other factors during the week preceding the exacerbation, SHS exposure was not reported for this period.
Taken together, the current evidence suggests that SHS exposure can cause asthma exacerbation among adults. Although there are fewer studies than in children, the data consistently link SHS exposure with poorer asthma status among adults with the condition. Based on the available literature, adults with asthma should avoid SHS exposure.

Examination of the Bradford Hill criteria supports a causal association between SHS exposure and exacerbation of adult asthma. Several studies demonstrated an exposure-response relationship between SHS exposure exacerbation of adult asthma [16,53,61,63] The temporal relationship between SHS exposure and the development of asthma or asthma-like symptoms was clearly delineated in most studies, especially the longitudinal cohort studies. Biologic plausibility is supported by the fact that SHS includes potent respiratory irritants and immunogens; exposure has been linked to greater bronchial hyper-responsiveness [15,62]. The consistency of study findings also supports a causal relationship between SHS exposure and asthma morbidity. In samples drawn from different populations, ranging from clinical to population-based samples, SHS has been consistently linked with poorer asthma status. The relationship between SHS exposure and asthma has also been observed in a variety of study designs, including cross-sectional, case-controlled, and cohort studies. The studies reviewed also demonstrate coherence in the association between SHS exposure and exacerbation of adult asthma. SHS exposure has been associated with an adverse impact on a variety of asthma outcomes, including diverse endpoints, such as respiratory symptoms, pulmonary function, and hospitalization for asthma. Taken together, the evidence is consistent with a causal effect of SHS on adult asthma exacerbation.

Summary

The long-term health consequences of SHS exposure have been established over the past two decades. Consistent epidemiologic evidence links SHS exposure with serious chronic health effects, including lung cancer and cardiovascular disease [3,65,66]. In the present article, the evidence suggests a causal relationship between SHS exposure and new-onset asthma and asthma exacerbation among adults. Despite the growing knowledge of SHS-related health effects, smoking is still permitted in many public locations and workplaces [67,68]. Because asthma is a visible condition among the general public, the evidence linking SHS exposure with adverse asthma health outcomes should provide policymakers with additional impetus for regulating public smoking and creating smoke-free public environments.

References


Jindal SK, Gupta D, Singh A. Indices of morbidity and control of asthma in adult patients exposed to environmental tobacco smoke [see comments]. Chest 1994;106(3):746–9.


The etiology and morbidity associated with asthma are thought to stem from both genetic factors and potentially modifiable environmental factors, such as viral infections [1–7]. Although it is unclear whether respiratory viral infections cause asthma, observational studies have demonstrated a high rate of asthma in children with a history of severe viral lower respiratory tract infections (LRTIs) during infancy, and viruses are associated with the majority of asthma exacerbations among both children and adults. This article discusses the pathogens associated with virus-induced wheezing illnesses during infancy and early childhood, the association of bronchiolitis during infancy with an increased risk of childhood asthma, and the association of respiratory viruses with asthma exacerbations in older children and adults.
Respiratory viral-induced wheezing illnesses in young children

Overview

Viral bronchiolitis is a LRTI typically associated with cough, tachypnea, retractions, and diffuse wheezing and rales [8,9]. Bronchiolitis is a leading cause of hospitalizations in the first year of life, accounting for an estimated 120,000 infant hospitalizations annually [10]. In infants, the etiologic agents of bronchiolitis and other viral respiratory infections associated with wheezing include respiratory syncytial virus (RSV), rhinovirus, influenza, parainfluenza (PIV), adenovirus, and more recently identified viruses, such as human metapneumovirus (hMPV) and human boca virus (hBoV) [11–14]. RSV causes epidemics of bronchiolitis and typically circulates in temperate climates during November to April with peaks in the winter months [11,15,16]. In tropical climates, peaks are related to temperature and level of rainfall [17]. RSV infects the majority of children during their first year of life and essentially all children show evidence of RSV infection by age 3 years [18]. The initial RSV infection is typically the most severe, causing lower respiratory tract disease, such as bronchiolitis, in 20% to 30% of infants [11,18,19]. Other viruses such as rhinovirus, PIV, and adenovirus circulate nearly year-round with seasonal peaks of illness [10,11,19,20].

Although RSV has long been identified as the major cause of infant bronchiolitis, the use of molecular techniques, such as polymerase chain reaction (PCR) assays, has allowed for more sensitive detection of rhinovirus and other viruses in respiratory infections [21,22]. Rhinovirus, which circulates year-round with major peaks during the autumn and spring, is a leading cause of upper respiratory tract infections, and most children show evidence of having had a rhinovirus infection by age 2 years [23–27]. Although, rhinovirus historically was thought to be limited to the upper respiratory tract, investigations have demonstrated that rhinovirus can infect the lower airways, is associated with infant bronchiolitis, and becomes a more dominant pathogen in wheezing illness as children get older [13,28–30].

Viral pathogens associated with bronchiolitis and wheezing illnesses in young children

Observational studies have described the viral etiology of bronchiolitis and wheezing illnesses in infants and very young children (Table 1) [11–14,19,20,31–39]. The first descriptive studies of the viral etiology of bronchiolitis in the 1960s through the 1980s primarily used such detection methods as cell culture, antigen detection, and serologic testing. Kim and colleagues [11] studied the epidemiology of RSV infection in infants and young children admitted to a children’s hospital in Washington, D.C., from 1960 to the mid-70s and found that 40% of children with bronchiolitis had evidence of infection with RSV. In a Norwegian study from 1972 to 1979, the investigators used immunofluorescence and cell culture to
investigate the epidemiology of respiratory viruses in young children admitted to the hospital with respiratory illness [31]. Of the 979 infants diagnosed with a respiratory virus infection, RSV accounted for 58% of all diagnosed infections, and 87% of RSV infections were associated with lower respiratory tract illness. The study also described the typical distribution of known viruses at the time, including the winter epidemics of RSV, influenza in the late winter and spring, and the seasonal distribution of rhinovirus with peaks in the autumn and spring [31]. Using multiple virus detection methods, including PCR, Jartti and colleagues [34] investigated the etiology of wheezing illness in 293 hospitalized children in Finland from September 2000 through May 31, 2002. Of the 76 infants studied, RSV (54%) was the most common virus detected, followed by picornavirus (42%) and hMPV (11%). Calvo and colleagues [36] studied consecutive respiratory admissions of 382 children less than 2 years of age to a single hospital in Spain from September 2003 to July 2005. Nasopharyngeal samples were obtained from 340 children and virus was isolated in 244 (71.7%) of the subjects. Of these, RSV accounted for 41.5%, rhinovirus 34.8%, adenovirus 8.3%, influenza 6.5%, and hMPV 5.9%. In children in whom rhinovirus was detected, recurrent wheezing and bronchiolitis were the leading diagnoses.

**Birth cohorts**

Cohorts of children recruited at birth have allowed longitudinal follow-up of children, including those with less severe disease who did not require hospitalization. In the Tucson Children’s Respiratory Study, a birth cohort of 1179 infants enrolled May 1980 to January 1985, Wright and colleagues [37] described the epidemiology of LRTIs during infancy. Overall, 80% of infants were followed through the first year of life. In total, 348 children contributed 460 LRTIs evaluated by physicians, with 292 respiratory cultures obtained at the initial illness. The cumulative incidence rate of lower respiratory tract illnesses in the first year of life was 32.9 per 100 children. One percent of infants were hospitalized for their illness. Immunoﬂuorescence and viral culture were employed to detect infection by RSV; PIV types 1, 2 and 3; influenza A and B; adenovirus; enterovirus; cytomegalovirus; and rhinovirus. An infectious agent was identified by viral culture in 193 of 292 (66%) available samples obtained from infants with lower respiratory tract illness. RSV accounted for 65% of the 183 first bronchiolitis diagnoses [37]. Other viruses detected in infants with bronchiolitis diagnoses included PIV types 1, 2, and 3 (14%); influenza A and B (4%); and adenovirus (2%).

An Australian cohort of 263 infants with at least one parent with doctor-diagnosed atopy, recruited infants from July 1996 to July 1999 and followed them through the first year of life [38]. Nasopharyngeal aspirates and detailed information were collected prospectively during acute respiratory illnesses and PCR was used to identify viral respiratory pathogens. Acute respiratory illnesses associated with wheeze or “rattly chest” were classified
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<td>Nasopharyngeal aspirate for viral culture, immunofluorescence, enzyme immunoassay, and/or PCR</td>
<td>RSV, PIV types 1–3, influenza A and B, adenovirus, enteroviruses, coronavirus, hMPV, rhinovirus</td>
<td>In children 3–11 mo: RSV (54%), respiratory picornaviruses (42%), hMPV (11%)</td>
</tr>
<tr>
<td>Williams et al [12]</td>
<td>1976–2001</td>
<td>248 of 341 specimens from lower respiratory tract illnesses with no known cause from children birth to 5 years</td>
<td>Nasal wash specimens for PCR</td>
<td>HMPV</td>
<td>HMPV detected in 20% of samples from previously negative lower respiratory tract illnesses</td>
</tr>
<tr>
<td>Kusel et al [38]</td>
<td>Birth cohort enrolled 7/1996–7/1999 and followed through first year of life.</td>
<td>263 infants (with a parent with atopy) during acute respiratory infections</td>
<td>Nasopharyngeal aspirates for PCR</td>
<td>RSV, PIV types 1–3, influenza A and B, adenovirus, coronaviruses, hMPV, rhinovirus, and other picornaviruses</td>
<td>Rhinovirus detected in 45.3% of “wheezy” LRTIs; RSV in 16.8%</td>
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<td>Kesebir et al [14]</td>
<td>1/2004–12/2004</td>
<td>425 respiratory specimens from children &lt;2 y submitted to clinical virology laboratory direct fluorescent antibody–negative for RSV, PIV, influenza A and B, and adenovirus during clinical visits/admissions; 96 nasal wash specimens asymptomatic children</td>
<td>Respiratory specimens for PCR</td>
<td>HBoV</td>
<td>HBoV detected in 5.2% of 425 respiratory specimens and 10% of hBoV-positive specimens associated with wheezing; no HBoV detected in asymptomatic controls</td>
</tr>
<tr>
<td>Miller et al [13]</td>
<td>10/2000–9/2001</td>
<td>592 children &lt;5 y hospitalized with respiratory symptoms or fever</td>
<td>Nasopharyngeal and throat specimens for viral culture, immunofluorescence, and/or PCR</td>
<td>RSV, PIV types 1–3, influenza A and B, hMPV, picornavirus (rhinovirus and enterovirus)</td>
<td>Virus detected in 61% of samples: rhinovirus (26%), RSV (20%), influenza (3%), PIV (7%), hMPV (3%), enterovirus (2%)</td>
</tr>
<tr>
<td>Calvo et al [36]</td>
<td>9/2003–7/2005</td>
<td>340 of 382 children &lt;2 years admitted for “respiratory tract infection”</td>
<td>Nasopharyngeal aspirate for viral culture, immunofluorescence, and/or PCR</td>
<td>RSV; PIV types 1–3; influenza A, B, and C; adenovirus; coronaviruses; enteroviruses; rhinovirus; hMPV</td>
<td>25% of hospitalized children &lt;2 y rhinovirus-positive. Of positive viruses: RSV (41.5%), rhinovirus (34.8%), adenovirus (8.3%), influenza (6.5%), hMPV (5.9%)</td>
</tr>
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as LRTIs. Of the 329 LRTIs, 28.9% were associated with wheeze. Rhinovirus was isolated in 45% of “wheezy” LRTIs, and RSV in 16.8%.

**Newly identified respiratory viruses**

The role of newly identified viruses, such as hMPV and hBoV, in infant wheezing illnesses is still being defined [12,14,40–42]. Williams and colleagues [12,43] investigated the role of hMPV in LRTIs in children enrolled at birth and followed to age 5 years in a vaccine clinic. HMPV, first identified in 2001, was detected in 20% of 248 available samples obtained from children with lower respiratory tract illness in which no respiratory pathogen was previously detected. HMPV therefore accounted for 12% of lower respiratory tract illnesses in this cohort of otherwise healthy young children [12,43]. Kesbir and colleagues [14,44] used available respiratory specimens submitted to a hospital-based clinical virology laboratory (January to December 2004) to investigate the prevalence of hBoV, first identified in 2005. HBoV was detected in 5% of the study samples obtained from children less than 2 years of age and negative for other viruses, although testing for rhinovirus was not performed. Wheezing illness was associated with approximately 50% of the hBoV-associated cases [14]. Allander and colleagues [42] found hBoV as the sole virus isolated in approximately 5% (12 of 259) of respiratory samples from children under 3 years of age who were hospitalized with acute wheezing. In general, the use of sensitive molecular techniques has confirmed the major role of RSV in infant bronchiolitis, broadened the role of viruses that were previously difficult to detect by culture, and allowed for the identification of new respiratory viruses. Furthermore, studies using PCR have demonstrated that while RSV appears to be the virus most commonly associated with wheezing in infants, rhinovirus plays a more prominent role after the age of 2 to 3 years [30,45].

*The increasing importance of rhinovirus in wheezing illnesses in older children*

Epidemiologic studies in infants and children have highlighted the importance of RSV-associated wheezing in infants and rhinovirus-associated wheezing in older children [30,45,46]. Rakes and colleagues [30] conducted a cross-sectional study of 70 children who presented to the emergency department with wheezing between January 1993 and April 1994, and compared them with 59 controls who presented to the emergency department with nonrespiratory complaints over the same period. Respiratory viruses were isolated in over 82% of the wheezing children less than 2 years of age. RSV was the most common virus detected in children less than 2 years of age (68%) and was not detected in any control subjects. However, in the children less than 2 years of age, similar proportions of nasal aspirates from those with wheezing and controls were positive for rhinovirus (41%). In the children older than 2 years, viruses were detected in 83% of wheezing
children. Rhinovirus was detected by PCR in 71% of the wheezing older children compared with 36% of the nonwheezing controls. RSV was detected in 6% of the wheezing children who were 2 years or older. In addition, the investigators found that 48% of the wheezing children who were 2 years or older had a positive test for rhinovirus and a measured marker of atopy compared with only 5% of the respective control group. In a similar 1-year study (2000–2001), 133 children (2 months to 18 years) admitted to the hospital for wheezing were compared with 133 age-matched controls admitted without wheezing [45]. In the younger children, virus was detected in 84% of the wheezing children compared with 54% of the respective controls. Consistent with other studies, RSV was the predominant virus in the younger children during the winter. However, rhinovirus was detected more frequently in young children hospitalized for wheezing from April through November. Among children older than 3 years, a respiratory virus was significantly more likely to be detected in children admitted for wheezing, than children without wheezing. Rhinovirus detection was significantly associated with wheezing. In addition, wheezing was strongly associated with atopy, as measured by total IgE and skin testing, in the children older than 3 years. These studies highlight the different pathogens associated with wheezing illnesses by age and the association of rhinovirus and atopy with wheezing in children beyond infancy.

The association of viral-associated wheezing illnesses during infancy and subsequent childhood asthma

Overview

The association between bronchiolitis during infancy and the development of asthma has been an area of interest for decades [4,47–74]. Most, but not all, previous studies have primarily included case infants who were hospitalized with bronchiolitis during infancy. Therefore, studies examining wheezing only after hospitalization for bronchiolitis during infancy may not reflect the outcomes of the large majority of infants with bronchiolitis who have only outpatient visits, emergency department visits, or no health care visit at all [75]. Although several early studies focused solely on RSV bronchiolitis or were conducted before routine testing for rhinovirus was available, more recent studies have used PCR to investigate the association of non-RSV bronchiolitis and subsequent wheezing [62,66,69,70,74,76,77]. Therefore, the diverse group of research investigations in this area includes case infants in whom the specific viral agents of bronchiolitis were not determined, case infants with only RSV bronchiolitis, and case infants with either RSV or non-RSV bronchiolitis. Overall, there is convincing evidence from several cohorts that RSV and rhinovirus bronchiolitis during infancy are risk factors for or markers for subsequent wheezing within the first decade of life [47,55,65–67,69–71,74].
Hospitalization for bronchiolitis during infancy and the association with recurrent wheezing and asthma during childhood

Respiratory syncytial virus bronchiolitis

Because RSV is known to be a major cause of bronchiolitis during infancy, several early cohorts included case infants who were hospitalized with RSV bronchiolitis during infancy [65,70,71,78]. Sigurs and colleagues [70,71] studied the relationship between RSV hospitalization during infancy and asthma in a small cohort of Swedish children. This prospective study included 47 children hospitalized with RSV bronchiolitis during infancy and 93 matched controls. The investigators defined the study outcomes as “asthma” (three or more episodes of bronchial obstruction verified by a physician), “recurrent wheezing” (three or more episodes of bronchial obstruction not physician verified), and “any wheezing” (asthma, recurrent wheezing, or one or two episodes of wheezing). At age 7.5 years, approximately one third of children with a history of severe RSV bronchiolitis were diagnosed with asthma and these children were significantly more likely to have a diagnosis of asthma than their nonhospitalized controls [70]. Though the cohort was small, the evidence from this study points to the likelihood of increased risk of asthma through age 13 among children who have a history of severe RSV bronchiolitis during infancy [71].

Respiratory syncytial virus bronchiolitis and non–respiratory syncytial virus bronchiolitis

Historical data also demonstrate the increased risk of wheezing or asthma after non-RSV bronchiolitis and emerging data suggest that children with a history of LRTI with viruses other than RSV may have an even greater risk of subsequent wheezing. As early as the 1960s, in a study of hospitalized children less than 5 years of age, Simon and Jordan [79] speculated that children with non-RSV bronchiolitis had a predisposition to develop asthma. Murray and colleagues [68] conducted an investigation of 73 children with either RSV or non-RSV bronchiolitis hospitalization during infancy and a retrospectively recruited nonhospitalized control group. The investigators found that the children hospitalized for bronchiolitis during infancy were more likely than controls to have wheezing (42.5% versus 15.0%) at 5.5 years [68]. In addition, wheezing by parent report (34% versus 13%) and use of bronchodilators (33% versus 3%) at 9 to 10 years after the initial bronchiolitis episode were more common in children with a history of a bronchiolitis hospitalization [47]. Fjaerli and colleagues [67] found that a group of 57 children hospitalized with bronchiolitis during infancy, whether RSV-positive or RSV-negative, were more likely to be under a doctor’s care for asthma at age 7, compared with a retrospectively recruited, nonhospitalized control group of 64 children. Piippo-Savolainen and colleagues [80] also found that children hospitalized for bronchiolitis in the first 2 years of life were more likely to have asthma in young adulthood. In a subset of participants,
Piippo-Savolainen and colleagues [63] found that adults with a history of non-RSV bronchiolitis during the first 2 years of life were at greater risk of developing asthma than were comparable adults with a history of RSV bronchiolitis. In a cohort of 81 children, Kotaniemi-Syrjänen and colleagues [66] investigated the relationship of non-RSV bronchiolitis during the first 2 years of life and the subsequent risk of asthma around age 7 years. They found that a rhinovirus-positive hospitalization for wheezing during the first 2 years of life was associated with a fourfold increased risk of asthma around age 7 years, compared with nonrhinovirus hospitalizations. Finally, Garcia-Garcia and colleagues [62] found an increased risk of early childhood asthma in children previously hospitalized with hMPV (23 children) or RSV (32 children) bronchiolitis compared with a control group hospitalized with gastroenteritis (38 children). Overall, this data suggests that viral LRTI with viruses other than RSV are associated with as high or even higher risk of childhood asthma than RSV-associated LRTI.

**Birth cohorts**

A limited number of longitudinal investigations of viral infections during infancy and subsequent wheezing have followed infants from birth, with the goal of prospectively identifying and investigating the spectrum of acute respiratory illnesses during infancy and early childhood on the risk of developing asthma [69,74,81]. These studies have allowed for the investigation of the association of viral LRTI that did not require hospitalization with subsequent wheezing. In the cohort of children enrolled at birth in the Tucson Children’s Respiratory Study, Stein and colleagues [4,69] found that children with a history of RSV LRTI in the first 3 years of life were 3.2 times more likely to have parental report of infrequent wheeze (one to three episodes of wheezing in past year) and 4.3 times more likely to have frequent wheeze (more than three episodes of wheezing in the past year) at 6 years, compared with infants with no LRTIs in the first 3 years of life. However, the association of RSV LRTI during infancy and infrequent and frequent wheeze decreased with age and neither was significant at age 13 years. At age 13 years, 517 of the 888 children (58%) followed for the first 3 years of life were included. The investigators suggested that, although RSV LRTI during early childhood was a risk factor for recurrent wheezing, it was not a risk factor for atopic asthma.

Lemanske and colleagues [74] found that a rhinovirus wheezing episode during infancy was the strongest predictor of persistent wheezing in preschool years among children enrolled in the Childhood Origins of Asthma Study (COAST). The COAST cohort is different from the Tucson cohort in that it includes only children with an increased risk of developing asthma [2]. All of the children in the cohort have at least one parent with respiratory allergies or physician-diagnosed asthma. The investigators found that children with at least one moderate to severe rhinovirus-associated wheezing illness during infancy had a 6.6-fold greater chance of subsequent wheezing...
in the third year of life and those with RSV had a threefold greater chance of wheezing in the third year of life [74]. In the combined moderate-severe illness group without wheezing, there was an increased risk for wheezing in the third year of life (odds ratio 3.9; 95% CI 1.1–15). This study is the first to show that, particularly in genetically susceptible hosts, even moderate to severe viral infections during infancy that are not associated with wheezing or hospitalization are associated with an increased risk of subsequent wheezing [74]. In another birth cohort of infants at high risk for asthma development, Kusel and colleagues [81] found that children with a history of “wheezy” LRTI infections with rhinovirus or RSV during infancy were at increased risk of having wheezing at age 5 years.

**Respiratory viral infections and acute asthma exacerbations**

**Overview**

A number of epidemiologic approaches have been employed to study the relationship between viral infections and asthma exacerbations (Table 2) [82–90]. These approaches include comparing the prevalence of respiratory viruses detected in asthma patients with and without acute exacerbations, and comparing virus detection in patients with asthma to that in patients without asthma in community, emergency department, or hospital settings. In general, many studies before the use of sensitive molecular techniques detected lower rates of viral infection during acute asthma exacerbations [83,87,88,91–93]. More recently, the use of PCR has resulted in increased detection of respiratory viruses in patients with asthma exacerbations [94].

**Asthma exacerbations in children**

Viruses are important triggers of asthma exacerbations in children and have been detected in up to 80% to 85% of exacerbations in children in studies using PCR for viral detection (see Table 2) [30,45,83,88,94–96]. Johnston and colleagues [94] investigated the association of viral infections and asthma exacerbations in a 13-month longitudinal study of 108 9- to 11-year-old English children with reported wheeze or persistent cough. Families recorded twice-daily peak flows and daily respiratory symptoms. Lower respiratory symptoms were defined and recorded as cough (day or night), wheeze (day or night), difficulty breathing or shortness of breath, or not fit to go to school because of chest problems. Viruses were detected in approximately 80% of reported episodes of LRTIs with associated decreases in peak flow measurements. Picornaviruses, which include rhinovirus and enteroviruses, accounted for two thirds of the positive samples. As a comparison, the investigators tested respiratory aspirates for picornavirus from the group of 65 children who provided a respiratory sample when they were asymptomatic. The investigators found that 12% of these samples were positive. In another investigation, Johnston and colleagues [97] found strong
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<tr>
<td>McIntosh et al [83]</td>
<td>Longitudinal follow-up 10/1967–5/1968 (group 1) or 10/1968–4/1969 (group 2)</td>
<td>32 children with history of “severe recurrent reversible obstructive airways disease” hospitalized during observation period</td>
<td>Nasopharyngeal and throat swabs for viral and bacterial culture and/or serology</td>
<td>RSV, PIV types 1–3, influenza A and B, adenovirus, and coronavirus</td>
<td>33% (group 1) and 51% (group 2) of wheezing episodes associated with proven respiratory infection</td>
</tr>
<tr>
<td>Minor et al [84]</td>
<td>Longitudinal follow-up 10/1971–5/1972</td>
<td>16 children with ≥4 “attacks of asthma” in previous year</td>
<td>Daily record of symptoms, twice-weekly examinations with nasopharyngeal viral and mycoplasma samples, monthly bacterial</td>
<td>PIV, influenza A and B, adenovirus, enterovirus, rhinovirus</td>
<td>42 of 61 episodes of asthma associated with a symptomatic respiratory infection</td>
</tr>
<tr>
<td>Minor et al [88]</td>
<td>Longitudinal follow-up 10/1971–5/1972</td>
<td>16 children with asthma and 15 siblings without asthma</td>
<td>Nasopharyngeal and throat swabs twice weekly for viral detection, monthly bacterial, quarterly blood samples</td>
<td>RSV, PIV, influenza A and B, adenovirus, enterovirus, rhinovirus</td>
<td>54 versus 35 episodes of viral infections asthma versus nonasthma. Children with asthma with more symptomatic rhinovirus infections</td>
</tr>
<tr>
<td>Mitchell et al [87]</td>
<td>Enrolled Jan–March 1975 and follow-up for 1 year</td>
<td>16 children with pre-enrollment history of ≥3 “wheezing attacks” in previous year</td>
<td>Nasopharyngeal and throat swabs for viral culture at respiratory illness and every 6 wk.</td>
<td>RSV, PIV, Coxsackie, adenovirus, enterovirus, and rhinovirus</td>
<td>91 of 127 captured episodes of wheezing: 14% virus isolation rate; rare virus isolation during asymptomatic testing</td>
</tr>
<tr>
<td>Carlsen et al [82]</td>
<td>1/1981–1/1983</td>
<td>169 children ≥2 y (256 exacerbations) with asthma seen in study hospital</td>
<td>Nasopharyngeal specimens for immunofluorescence and viral culture and/or serology</td>
<td>RSV, PIV types 1–3, influenza A and B, adenovirus, rhinovirus</td>
<td>Virus detected in 29% of asthma exacerbations (rhinovirus detected in 12.9% of all exacerbations)</td>
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<tr>
<td>Study</td>
<td>Design</td>
<td>Sample Size</td>
<td>Follow-up Period</td>
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<tr>
<td>Corne et al [110]</td>
<td>Longitudinal</td>
<td>76</td>
<td>9–12/1993</td>
<td>Nasal aspirates for PCR</td>
<td>Rhinovirus</td>
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<tr>
<td>Tan et al [107]</td>
<td>Acute and quiescent (4–6 wk) viral detection</td>
<td>17 patients with near-fatal asthma; 29 acute asthma; 14 with chronic obstructive pulmonary disease</td>
<td>Tracheal aspirates near fatal asthma; induced sputum in patients with acute asthma or chronic obstructive pulmonary disease for PCR</td>
<td>Picornavirus, RSV, PIV, influenza A and B, adenovirus</td>
<td>Viral detection in 52% of acute episodes and 7% of quiescent</td>
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<tr>
<td>Thumerelle et al [99]</td>
<td>Recruited 10/1998–6/1999</td>
<td>82 children with active asthma admitted with exacerbation versus 27 asymptomatic children with asthma</td>
<td>Nasal secretions for PCR, immunofluorescent assay, and/or serology</td>
<td>RSV, PIV types 1–3, influenza A and B, adenovirus, coronavirus, picornavirus (rhinovirus and enterovirus)</td>
<td>Viruses detected in 38% of children with exacerbations versus 3.7% children without exacerbation</td>
</tr>
<tr>
<td>Johnston et al [96]</td>
<td>Recruited 9/10–9/30 2001</td>
<td>Children with asthma presenting either to emergency department (57 cases) or community recruits (157 controls)</td>
<td>Spontaneous or nasal wash samples for PCR</td>
<td>RSV, PIV types 1–3, adenovirus, influenza A and B, coronavirus, picornavirus (rhinovirus)</td>
<td>Viruses detected in 62% cases versus 41% controls</td>
</tr>
<tr>
<td>Williams et al [108]</td>
<td>12/1999–12/2003 acute and quiescent (3 mo) viral detection</td>
<td>101 adults hospitalized with asthma</td>
<td>Nasal wash specimens for PCR</td>
<td>HMPV</td>
<td>HMPV detected in 6.9% of acute hospitalizations and in 1.3% at follow-up</td>
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<tr>
<td>Vernarske et al [109]</td>
<td>12/1999–12/2003 acute and quiescent (3 mo) viral detection</td>
<td>101 adults hospitalized with asthma</td>
<td>Nasal wash specimens for PCR</td>
<td>Rhinovirus</td>
<td>Rhinovirus detected in 21% acute hospitalization and in 1.3% at follow-up</td>
</tr>
<tr>
<td>Khetsuriani et al [98]</td>
<td>Recruited 3/2003–2/2004</td>
<td>Children with persistent asthma with asthma exacerbation (65 cases) and well-controlled asthma (77 controls)</td>
<td>Nasopharyngeal and throat swabs for PCR</td>
<td>RSV, PIV types 1–3, influenza A and B, adenovirus, HMPV, picornaviruses (rhinovirus and enteroviruses)</td>
<td>Viruses detected in 63.1% of cases versus 23.4% of controls</td>
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correlations between the rates of upper respiratory tract infections, divided in half-monthly segments, and rates of pediatric and adult hospital admissions for asthma as determined by *International Classification of Diseases, Ninth Revision* codes. These studies demonstrate the high prevalence of respiratory viruses in children with asthma and the correlation of peaks in respiratory infections with asthma hospitalizations.

The New Vaccine Surveillance Network is a population-based surveillance investigation of hospitalized pediatric patients ages birth to 5 years from two United States counties [13]. Based on the 592 children enrolled October 2000 through September 2001, children with a history of wheezing or asthma had significantly higher estimated rates of rhinovirus-associated hospitalizations (25.3 of 1000 children) than those without a history of wheezing or asthma (3.1 of 1000 children) \( P < .001 \).

**Prevalence of virus detection in children with and without asthma exacerbations**

Other investigations have examined the relationship between respiratory virus infection and asthma exacerbations by comparing virus detection in asthma patients with and without an acute exacerbation [98,99]. Thumerelle and colleagues [99] conducted a regional study of 82 French children (October 1, 1998, through June 30, 1999), aged 2 to 16 years. In children with asthma, the investigators found higher rates of virus detection among those hospitalized with an exacerbation compared with those without an exacerbation in the prior 3 weeks. Khetsuriani and colleagues [98] studied children aged 2 to 17 years with persistent asthma. Sixty-five children with acute asthma exacerbations and 77 children with well-controlled asthma were enrolled. One or more viruses were detected in 63% of the patients with asthma exacerbations and in 23.4% of the patients with well-controlled asthma. Rhinovirus was detected among 60% of case patients and 18% of controls. Symptomatic respiratory infections positive for at least one virus were associated with asthma exacerbations, while asymptomatic infections were not.

*The September epidemic of asthma*

Observational studies have also been used to investigate the association of respiratory viruses with asthma morbidity. An increase in asthma hospitalizations during early autumn has been noted in several countries, and respiratory viruses, in particular rhinovirus, have been speculated as causative agents [24,90,100–102]. Johnston and colleagues [96] investigated the etiology of the “September epidemic of asthma exacerbations” in a case group of 57 Canadian children with asthma who presented to the emergency department during the last 3 weeks of September compared with a group of 157 controls with asthma recruited from the community. Although the control group did not have an emergency department visit, a majority reported asthma symptoms, including continuous or repeated breathing trouble,
waking at night, and activity limitations. Viruses were detected in a significantly larger proportion of the children presenting to the emergency department than children who did not present to the emergency department (62% versus 41%). Cases were also less likely than controls to have been prescribed an inhaled corticosteroid. In a separate study, Johnston and colleagues [103] used a mathematical model to investigate the relationship between peak asthma hospitalizations in Canada and the return to school. The investigators found that over the 13 study years, the average timing of the peak of asthma hospitalizations in school-age children occurred 17.7 days following the return to school, with later peaks for preschool children and adults. The investigators concluded that school-age children were the likely source of the etiologic agent resulting in the yearly peak in asthma hospitalizations, with a plausible hypothesis being transmission of such infectious agents as rhinovirus.

**Asthma exacerbations in adults**

**Respiratory virus detection in adults with asthma**

Viruses are important triggers of asthma exacerbations in adults, and studies using PCR have detected viruses in approximately 40% to 50% of exacerbations (see Table 2) [89,91,104–106]. A study by Teichtahl and colleagues [104] included adults admitted for asthma exacerbations and matched controls admitted for elective surgery, August 1993 to July 1994. Seventy-nine patients with asthma and 54 controls were included. Overall, 37% of the adults admitted with asthma had a virus detected compared with 9% of the control group. Atmar and colleagues [105] conducted a longitudinal study of 29 adults with asthma recruited from pulmonary clinics and a cross-sectional study of a convenience sample of 148 adults who presented to the emergency department with an asthma exacerbation. Viruses were detected using virus-specific PCR. The investigators found that, in the longitudinal study, 44% of asthma exacerbation were associated with a respiratory tract viral infection. In the cross-sectional emergency department study, 55% were associated with a viral infection. Rhinovirus, coronavirus, influenza, and PIV were the most common viruses detected.

**Prevalence of virus detection in adults with asthma during exacerbations and quiescence**

Several studies have performed viral detection both during asthma exacerbations and subsequent follow-up. Using PCR, Tan and colleagues [107] investigated the prevalence of viral respiratory infections in 17 adults with near-fatal asthma requiring ventilatory support, 29 adults hospitalized with an asthma exacerbation, and 14 hospitalized with chronic obstructive pulmonary disease. Samples for viral detection were taken during the acute asthma exacerbation and follow-up samples were obtained 4 to 6 weeks after hospital discharge. During the acute exacerbation, 52% of the overall samples were
positive, including 59% of the near-fatal asthma and 41% of the acute exacerbations. In the near-fatal asthma group, 47% of the viruses detected were picornavirus and 24% were adenovirus. Viral detection was positive in 7% of the 29 specimens collected 4 to 6 weeks after hospital admission [107].

Other studies have used molecular diagnostic techniques to investigate the role of more recently discovered viruses in the pathogenesis of asthma exacerbations. Williams and colleagues [108] determined the prevalence of hMPV in a cohort of 101 adults at initial enrollment during an asthma hospitalization (1999–2003) and at follow-up 3 months later. HMPV was detected in 6.9% of subjects at admission compared with 1.3% in follow-up. Furthermore, none of the subjects positive for hMPV at admission were positive at follow-up [108]. Another study involving this cohort of patients described the prevalence of rhinovirus in patients during an acute asthma exacerbation and 3-month follow-up [109]. Over the 4-year study period, 21% of the cohort was rhinovirus-positive by PCR during the asthma exacerbation. Seventy-six of the 101 participants completed the 3-month follow-up. At follow-up, only 1.3% (1 patient) were positive and none of the subjects who were rhinovirus-positive during the preceding asthma exacerbation were positive at follow-up. Subjects who were rhinovirus-positive were more likely to smoke cigarettes and be nonusers of inhaled corticosteroids compared with rhinovirus-negative subjects, similar to the findings of lower use of inhaled corticosteroids among children seen in the hospital during the September asthma epidemic associated with rhinovirus [96,109].

Rhinovirus clinical lower respiratory tract infections in adults with and without asthma

Corne and colleagues [110] conducted a longitudinal investigation of rhinovirus infection by following 76 subjects with asthma and their cohabitating partners without asthma over a 3-month period (September through December 1993). Subjects maintained diaries of severity of upper and lower respiratory tract symptoms and nasal aspirates were obtained from subjects every 2 weeks. Overall, there were no differences in rhinovirus positivity between the subjects with and without asthma. However, the investigators found that participants with asthma had more frequent clinical LRTIs associated with rhinovirus than did controls (43% versus 17%, respectively). In addition, the group of patients with asthma had significantly higher severity scores (median 1 versus 0) and longer duration of illness (median 2.5 days versus 0 days) [110].

Summary

Epidemiologic investigations have provided valuable insight into the role of respiratory viruses in wheezing illnesses in children and adults. Viruses are the most important cause of LRTIs in infancy and early childhood, and LRTIs with respiratory viral pathogens have been identified as
significant risk factors for the development of early childhood asthma. RSV is an important pathogen in wheezing illnesses during infancy and appears to become less commonly associated with wheezing illnesses in older children. The newly appreciated role of non-RSV LRTI and the strong association of rhinovirus illness with a marked increased risk of future wheezing among children born to a parent with asthma suggest a differential “asthmagenicity” of respiratory viruses in asthma pathogenesis. Although it is unclear whether respiratory viruses induce asthma development, children with severe infections during infancy are at increased risk of subsequent wheezing, and large longitudinal studies will, it is hoped, help answer this critical question. Knowing whether respiratory viruses cause asthma presents the hope for a new strategy for asthma prevention. In addition, viruses, implicated in the vast majority of significant disease exacerbations, are important triggers of asthma exacerbations in children and adults, and respiratory viral illness prevention would likely decrease the significant morbidity related to this common chronic disease.

References


Occupational Exposures
and Adult Asthma
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Relationships between asthma and occupation

Adult asthma can relate to occupational exposures in several potential ways. First, adult asthma, especially if not well controlled, can reduce the ability of adults to perform their jobs effectively and lead to time off work [1–3]. Time may be lost from work if there is an exacerbation of asthma or if asthma is poorly controlled, even if it is not the result of work exposures. As an example, a manual worker with asthma who develops a respiratory viral infection with an associated exacerbation of asthma may not be able to exercise normally at that time, even for several weeks. An outdoor worker with asthma who has run out of or has not been appropriately prescribed inhaled asthma medications (in particular inhaled steroids) [3] may not be able to function well in cold or hot and humid weather.

Second, asthma can be caused by occupational exposures, termed occupational asthma (OA), or can be exacerbated or aggravated by occupational exposures, termed work-exacerbated asthma (WEA) or work-aggravated asthma. Although OA has been recognized and investigated for many years, exacerbation or aggravation of asthma from occupational exposures (although not a new phenomenon), in contrast, is a relatively new focus of research studies. This is considered a separate entity from OA because the job has not caused the new onset of asthma and the implications for workers’ compensation are different from those of OA—in many jurisdictions it is not compensable despite the fact that significant morbidity and socioeconomic impact can result from OA and from WEA [4–6]. OA and WEA can be included under the term, work-related asthma, yet even recently, most clinical guides have addressed only the subgroup with OA [7,8].

This article covers some aspects of epidemiologic studies of OA and reviews aspects of WEA to illustrate what has been learned from these studies.
This is not a comprehensive or systematic review of all published epidemiologic studies in this area. Studies of the effects of common asthma on the ability to work, on time missed from work, or job changes due to asthma are not reviewed in this article.

**Occupational asthma**

OA is reported as the most common chronic occupational lung disease in industrialized regions, especially with the decline in prevalence of pneumoconioses [9,10]. It has been defined as asthma resulting from causes and conditions attributable to a specific work exposure and not to causes outside the workplace. This is a clinical definition and assumes that clinical diagnostic tests are able to establish the probability of an occupational causation for asthma. In epidemiologic studies, the definition often is by necessity different from the clinical definition [11], usually based on (a) questionnaire findings with positive responses to questions about improvement of asthma symptoms away from work (weekends or holidays) as compared with working days; (b) a history of asthma symptoms or doctor-diagnosed asthma, starting during a working period; and (c) an exposure history consistent with a high-level irritant exposure (irritant-induced asthma or reactive airways dysfunction syndrome) or a history of exposure at work to an agent capable of causing respiratory sensitization and asthma. Such self-reported symptoms are relatively sensitive for a diagnosis of OA [12] among a population in a tertiary referral occupational lung clinic, and a positive exposure history is expected to add to the sensitivity, particularly for OA induced by a high molecular weight occupational allergen. Nevertheless, the specificity of self-reported features is low in comparison to a clinical gold standard of specific challenge tests. A history of wheezing worse at work and associated nasal and eye symptoms but absence of loss of voice is reported as having the best historical positive predictive value in a model derived from these factors (positive predictive value 74%) for OA induced by high molecular weight allergens [13] but no historical factors were reliable for predicting OA caused by low molecular weight allergens (to distinguish OA from WEA or other diagnoses) in that study.

Even within tertiary referral clinics, a proportion of patients referred for assessment of suspected work-related asthma does not have asthma but has other causes of work-related symptoms, such as vocal cord dysfunction, upper airway cough syndrome, or gastroesophageal reflux. In one tertiary referral clinic, 31% of those referred for assessment of possible OA had no objective evidence of asthma although still working with the implicated occupational exposure [14]. In addition, the first onset of asthma during a working period, despite being a typical characteristic of patients who have OA, is not specific, because the proportion of all adult asthma attributable to occupation is estimated at 5% to 19%, median 9% [15], implying that a majority of adult asthma begins coincidental to work exposures.
Therefore, considerations in epidemiologic studies assessing OA include (1) How confident is the diagnosis of asthma and has there been an additional objective measure to confirm asthma in addition to questionnaire responses? and (2) Can OA be distinguished from WEA? Although many epidemiologic studies use validated asthma questions [16,17], fewer include an objective measure to add to the certainty of diagnosis [17].

The addition of a methacholine challenge has been used in a subset in some population-based studies, such as the Canadian six-community study [18] and an international population study relating risks for new-onset asthma to occupation [19]. In the Canadian asthma study [18], a case definition of OA was derived from (1) exposure in a high-risk occupation and industry at the time of onset of asthma (considered probable OA) and (2) exposure to a substance that may cause OA but not being in a high-risk job at the time of onset of asthma (considered possible OA). The investigators also estimated the population-attributable risk for high-risk jobs and exposures. They reported a high prevalence of possible and probable occupational asthma, 36%, and a population-attributable risk for adult asthma in high-risk jobs and exposures of 18%. The international study [19] showed significant excess asthma risk from exposure to agents known to cause OA, especially among those who had asthma defined by symptoms and a positive methacholine response (ie, those who had objectively confirmed asthma [relative risk (RR) 2.4; 95% CI, 1.3–4]), illustrating the value of a more definite asthma diagnosis when possible in such studies. Risks also increased after reported inhalation accidents, consistent with irritant-induced asthma (RR 3.3; 95%, CI 1–11). In population epidemiologic studies, it is difficult to distinguish OA from WEA with certainty. Perhaps for that reason, some other population epidemiologic studies have reported “the occupational contribution to the burden of asthma” [20] rather than “occupational asthma.”

Other epidemiologic studies have focused on specific groups of workers who had relatively uniform exposure. For example, some studies have assessed workers exposed to high molecular weight allergens (such as workers in bakeries [21], workers in animal care facilities [22], enzyme-exposed workers [23], and snow crab workers [24]); those exposed to low molecular weight sensitizers (such as spray painters [exposed to diisocyanates] [25], red cedar workers [26], and workers exposed to complex platinum salts [27]), and others who have exposure to agents known to be respiratory sensitizers capable of causing OA. These studies have clarified the prevalence of OA related to various sensitizers and helped identify host and environmental risk factors, including atopy, smoking for some agents, and degree of exposure. Outcomes also have been determined in some studies. Some publications report incidence of sensitization and OA—for example, a series of prospective studies of apprentices in Quebec in pastry-making, animal care work, and dental assistants (with latex glove use) [28–30]. The effects of intervention, including primary, secondary,
and tertiary preventive measures, also have been assessed in various occupational settings [8,31,32].

Not all workers who have OA have a clearly identified workplace sensitizer, however, and in many workers there may be mixtures of potential sensitizers and irritant agents. Even in the examples described previously, animal care workers may wear powdered latex gloves and may have exposure to other dusts or endotoxin [33], which can be associated with symptoms; dental workers may be exposed to acrylic compounds; and auto-body workers may use paints or other compounds with sensitizers besides diisocyanates, such as epoxy compounds or amines.

Studies of workforces, such as hospital workers, have shown the potential for development of physician-diagnosed asthma from several causes in a single workplace. Many were assessed in a study by Delclos and colleagues [34], including medical instrument cleaning (odds ratio [OR] 2.22; 95% CI, 1.34–3.67), general cleaning (OR 2.02; 95% CI, 1.20–3.40), use of powdered latex gloves (only between 1992 and 2000) (OR 2.17; 95% CI, 1.27–3.73), and exposure to aerosolized medications (OR 1.72; 95% CI, 1.05–2.83). That study also used a second outcome measure, bronchial hyper-responsiveness–related symptoms, also based on symptoms alone, which had some different associations and may have included symptoms from mucous membrane irritation. The associations were with general cleaning (OR 1.63; 95% CI, 1.21–2.19), aerosolized medication administration (OR 1.40; 95% CI, 1.06–1.84), use of adhesives on patients (OR 1.65; 95% CI, 1.22–2.24), and exposure to a chemical spill (OR 2.02; 95% CI, 1.28–3.21). Studies such as this have shown the ability to assess temporal changes in the relationship of asthma to various sensitizers, in particular natural rubber latex in this study. Other studies, which have examined changes in sensitization and asthma from natural rubber latex in relation to changes in the use of powdered latex gloves, similarly showed significant declines as gloves have been changed to low-protein, low-powdered latex gloves or nonlatex gloves [35,36].

Cleaners are another group of workers who have a mixed exposure to potential respiratory sensitizers and irritants at work. They became a population of interest after initial population studies indicated increased confirmed asthma among cleaners in Spain and other European countries [37,38]. A series of epidemiologic studies have focused on cleaners and have shown some unexpected results [39–43]. Zock and colleagues [41] have shown that domestic cleaners are more likely to have asthma than other professional cleaners but, although they were more likely to be sensitized to dust mites (28%) than other professional cleaners (3%), they had a similar rate of dust mite sensitization as a control group of office workers. In addition, rather than showing an association of asthma with a recognized allergen (dust mites), asthma among domestic cleaners was associated mainly with kitchen cleaning and furniture polishing. In contrast, cleaners who were not domestic cleaners did not show an increased risk for asthma,
suggesting a specific relationship with domestic cleaning. In a case-control study, which included personal exposure measurements of chlorine and ammonia in a subset, domestic cleaners who had asthma had greater exposure to chlorine (more frequent use of bleach) than those who did not [40], and a subsequent panel study of domestic cleaners who had recent respiratory symptoms (asthma or chronic bronchitis) [39] showed symptoms associated mainly with bleach, degreasing sprays, and air fresheners. It may be expected that high-level accidental exposures, such as to mixtures of bleach and ammonia, might induce OA on an irritant basis (reactive airways dysfunction syndrome) and this might account for some of the increased asthma among domestic cleaners. It remains unclear at present whether or not chronic moderate concentrations of irritant agents can induce new onset of asthma or whether or not such exposures may cause the new onset or recurrence of symptoms in workers who have underlying airway hyperresponsiveness, which otherwise would be asymptomatic. Assessment of serial peak flow recordings in the panel study [39] showed that only a minority of symptomatic workers had peak flow changes suggestive of work-related asthma despite the associations with symptoms, suggesting that some of the work-attributed symptoms may have been based on mucous membrane irritation rather than asthmatic responses from this exposure.

These studies illustrate the difficulty in drawing diagnostic conclusions from epidemiologic occupational studies of asthma when a specific occupational sensitizer has not been identified. Among epidemiologic studies of workers, unless spirometry and methacholine tests are performed, it may be difficult to distinguish asthma from chronic bronchitis, and, without further diagnostic tests, may also be hard to differentiate between OA and WEA. Even when a specific sensitizer is present in the workplace, such as for laboratory animal workers, the concurrent presence of other agents, such as endotoxin and dust, can cause diagnostic confusion unless additional immunologic tests are included to determine whether or not there is sensitization to the known workplace allergens (for example laboratory animals) [33].

Other epidemiologic studies focusing on the course and outcome of OA may give insight into the natural history of asthma [44]. Several workplace sensitizers that cause asthma may not be encountered commonly outside the work environment; therefore, the effects of complete avoidance of exposure can be studied more easily than those of common environmental allergens, such as dust mite and cat allergens. Follow-up studies of workers who have sensitizer-induced OA have reported improvement in asthma symptoms, medication needs, and airway responsiveness to methacholine in a subset after removal from exposure to the relevant work sensitizer. Outcome, as reported in some studies, is better in patients who had initial milder asthma at the time of removal from exposure and a shorter duration of asthma at the time of removal [45,46]. Duration of follow-up and the reported results are not uniform between studies, however, and one systematic review concludes
that the studies were not sufficiently uniform for formal analyses although plotting of results suggested improvement from removal as compared with reduced or continuing exposure [47]. Another systematic review [48] showed a wide range of follow-up in published studies, but pooled estimates indicated a 32% symptomatic recovery rate with best outcome among younger subjects and those who had shorter duration of exposure. Nonspecific airway hyper-responsiveness persisted in 73% and this figure was higher among those sensitized to a high molecular weight occupational agent. The authors concluded, “The available data on the prognosis of OA are insufficiently consistent to allow confident advice to be given to patients with the disease” [48]. They recommend, “Clinicians and epidemiologists with an interest in this disease should consider a collaborative and carefully standardized study of the prognosis of occupational asthma” [48].

Ideally there would be more uniform follow-up of workers who have OA to better determine prognostic factors and allow identification of those workers who have OA who are likely to improve with complete future avoidance of a work sensitizer versus reduced exposure. There are significant socioeconomic impacts resulting from work changes due to OA [4,49,50] and it is important to identify if there are patients who have sensitizer-induced OA who may be managed with markedly reduced but not complete avoidance strategies, as is suggested for health care workers who have OA from natural rubber latex [51].

In an occupational setting, as indicated by Nicholson [52], it is unlikely to be feasible to perform randomized, double-blind, control studies for interventions, including removal or reduced exposure for workers who have OA. Similarly it often is difficult to assess the effects of individual components of primary and secondary preventive measures in an occupational setting because they usually are not performed in isolation as single intervention methods [31]. As an example, the removal of high-protein powdered latex gloves from a health care setting (a primary preventive measure) was accompanied by a medical surveillance program, including worker education and a questionnaire, skin testing for natural rubber latex (secondary prevention), and transfer of symptomatic sensitized workers away from areas where they might have direct contact with natural latex products (tertiary prevention) [36]. In addition, the effects of a medical surveillance program may differ in a “real life” work application as compared with effects during a research study, as illustrated in bakeries in the United Kingdom [21]. Nevertheless, it is hoped that high-quality epidemiologic studies can be developed to answer many of these questions remaining in OA.

**Work-exacerbated asthma**

There is no uniform definition of WEA (termed, in some studies, work-aggravated asthma) [6,53–56]. WEA is a term used to describe worsening of pre-existing asthma at work or the worsening of asthma at work when
asthma begins during a work period but is not believed to be caused by work (ie, it is considered to start coincidentally to work but then is exacerbated by work exposures). There is a wide range of severity and duration of exacerbations of asthma in epidemiologic studies of WEA. At one extreme, several have included exacerbations that are transient (often based on symptomatic worsening without any objective documentation) [55], and, at the other extreme, studies have included only prolonged symptomatic worsening that has presented with a clinical history similar to that of OA and has been diagnosed by the absence of a specific inhalation challenge response to a workplace sensitizer [4,56]. The source of cases also has influenced the severity; cases based on surveys of working asthmatics in a primary care setting [57] not surprisingly have reported exacerbations that are generally milder, of shorter duration, and less well documented than those from surveys of an occupational pulmonary tertiary referral clinic setting [4,56].

A few studies have included cases from workers’ compensation in a jurisdiction where WEA can receive compensation. These have included a mixture of cases initiated by primary care physicians, emergency physicians, occupational health care workers, and pulmonologists. A majority of compensated WEA cases have not been seen by a specialist but claims have been initiated from primary care and emergency visits, and the individuals have had transient worsening of symptoms attributed to a work exposure, often with few or no missed days from work [54,55].

The exposures that cause an exacerbation of asthma at work often are different from the causes of OA. Sensitizer-induced OA by definition is asthma caused by a specific work sensitizer, which may be a high molecular weight allergen (such as enzymes, animal, plant, or fungal allergens) associated with development of specific IgE antibodies or may be a chemical sensitizer, such as diisocyanates, epoxy compounds, or plicatic acid, for which the exact mechanism of sensitization may be unclear [58]. In contrast, the causative agent for WEA often is not a sensitizer but one or more asthma triggers, such as smoke, fumes, sprays, dusts, cold air, extremes of humidity, and frequently some combination of these [54,59]. Such agents are expected to trigger bronchoconstriction in subjects who have asthma to a varying extent depending at least in part on the degree of exposure, the severity and control of asthma at the time of exposure, and other potential factors. Additional agents that may be expected to exacerbate asthma at work include endotoxin [60] (for which there may be additional individual susceptibility in the response) [61,62]; common allergens, such as domestic animal or dust mite exposure in asthmatic domestic cleaners who are allergic to these [43]; and outdoor pollen or fungal exposures in outdoor workers on a seasonal basis. As discussed previously, Zock and colleagues [43] have shown that Spanish domestic cleaners are more likely allergic to dust mites than other professional cleaners despite relating their symptoms mainly to chemical cleaning agents, so it is difficult to determine whether or not those
sensitized domestic cleaners who have asthma should be classified as having WEA from a common allergen or from nonspecific irritant chemicals or true OA. Individuals who have increased work exposure to small children (teachers and daycare workers) or those in crowded settings may be expected to be at increased risk for respiratory viral infections likely leading to exacerbation of asthma. Potentially emotional stress at work also might contribute to an exacerbation of asthma symptoms. It also can be expected that there may be a combination of factors leading to an exacerbation, for example an asthmatic teacher who has a cold and who is asked to supervise children in outdoor activities on a cold day or a factory worker who has asthma and is exposed to dusts, fumes, and sprays at work on a day when the ventilation is malfunctioning.

Nevertheless, there is currently little information in published studies as to the background/baseline severity or level of control of asthma in those who have transient WEA and the exact exposure conditions that trigger the exacerbation. It is expected that asthmatic workers who have more severe asthma (associated with greater airway inflammation and greater airway hyper-responsiveness) are more likely to have an exacerbation of asthma at work under particular exposure conditions than asthmatics who have milder asthma. The use of asthma medications, however, also may modulate the response to work exposures that otherwise may exacerbate asthma—analogous to the prevention of bronchoconstriction from methacholine or cold/dry air or exercise challenge by pretreatment with bronchodilators [63] and to a lesser extent by pretreatment with inhaled steroids [64]. Lack of asthma control, as a result of insufficient environmental or pharmacologic management, or a recent respiratory viral infection might be expected to lead to greater susceptibility to exacerbation from asthma triggers in the workplace in the same way that it may increase the airway response to bronchoconstrictor agents, such as methacholine in the laboratory setting [63], but this has not been adequately assessed in epidemiologic studies of WEA to date.

Most epidemiologic studies on WEA have been based on questionnaire or self-reported responses [53,57,59]. As an example, Henneberger and colleagues [65] reported baseline findings from a longitudinal study of more than 500 working asthmatics enrolled in a single health maintenance organization. A telephone questionnaire was used to determine a work-related symptom score based on asthma symptoms, medications, and triggers. Their definition of WEA for their study was self-report of work-related worsening symptoms (symptom improvement on weekends and periods off work), increased medication needs on working versus nonworking days, and identification of exposures at work that seemed to trigger asthma symptoms. A probability rating was determined from these and from determination by an expert panel that there was a likely asthmagenic agent at work. A scoring system was developed for the probability of an exacerbating exposure using separate probability ratings for sensitizers and irritant agents and
including rating of frequency and intensity of likely exposure. Using these
criteria, they identified 61% of working men and 41% of working women
as having exposure to potential sensitizers or irritants at work. They identi-
fied 23% of the working asthmatics as having moderate or strong evidence
of WEA using their work-related symptom score and exposure score. These
workers more likely were men (45% versus 27%) and had more days in
which they were bothered by asthma in the week before the interview.
Among the approximately 200 who were employed when their asthma
started, 10% believed that it began as a result of work, which if correct is
considered OA (a percentage similar to the estimates of the burden of
asthma due to occupational exposures) [15,20]. This article [65] illustrates
the high prevalence of potential exacerbating factors at work for adults
who have asthma, and others also have identified a high frequency of symp-
tomatic worsening at work among asthmatics [66].

Another perspective can be gained from review of workers’ compensation
claims for WEA. Although such claims are not eligible for compensation in
many jurisdictions, they can be compensated in Ontario, Canada, as “work
aggravated asthma,” a separate category from “occupational asthma.” An
older review of compensated asthma claims in Ontario from 1984 to 1988
[54] showed that a similar number of claims was accepted for work-
aggravated asthma (used with the same meaning as WEA) as for OA during
that period. A more recent review has shown these accepted claims to
greatly exceed OA [67], with more than 80% from work-aggravated
asthma/WEA. A study including comparison of clinical investigations in
WEA and OA has shown that in contrast to the investigations usually avail-
able for OA to confirm the work relationship, in the majority of work-
aggravated asthma/WEA claims there is little objective confirmation
of the diagnosis—most were seen for a transient exacerbation of asthma
by a primary care physician or an emergency physician [55]. In contrast
to claims for irritant-induced OA (including reactive airways dysfunction
syndrome) most claims for work-aggravated asthma/WEA were for a short
period of time off work [68]. An illustration of this is the identification of
a large transient spike in asthma exacerbation claims from workers in
schools associated with a strike of maintenance workers and assumed
increased dust and indoor air pollution at that time [10]. These findings
are consistent with a recent report [69] that identified cases of work-related
asthma from the educational services industry as reported to four states in
the Sentinel Event Notification System for Occupational Risks (SENSOR).
Nine percent of all work-related asthma cases reported were from this indus-
trial sector, of which approximately one third were classified in their system
as work-aggravated asthma rather than new-onset asthma. Most cases were
teachers and teachers’ aides and the most common self-implicated exposures
for those who had WEA were to “mold,” “dust,” and “indoor air pollutants.” The amount of time missed from work and the duration of the
asthma “aggravation,” however, were not reported.
A proportion of individuals who have WEA may have more prolonged or consistent exacerbation of asthma at work such that the clinical history may be similar to OA with frequent worsening of symptoms on working days and improvement on weekends or holidays. These may fall into the category of more “definite” WEA in the study by Henneberger and colleagues [65]. This subgroup also may be the subjects more likely to be referred for investigation of possible work-related asthma to a specialist and to undergo more objective investigations to exclude OA from a sensitization: objective confirmation of a diagnosis of asthma, serial peak expiratory flow monitoring, methacholine challenge at the end of a work week and after a period off work, immunologic tests to assess a possible IgE antibody response to a work agent, and in some centers induced sputum and consideration of specific chamber challenge testing.

There are few studies that have reported findings from such a group who have undergone detailed investigation [4,6,56,70], and (as indicated previously), these are likely to represent a subgroup that has more prolonged and severe work-related symptoms. A specific chamber challenge test generally is undertaken only if OA is a possibility in the differential diagnosis and if there is a work exposure agent that might be a sensitizer. In these circumstances a patient who has a negative specific challenge but work-related asthma symptoms is regarded as having WEA. When defined in this way, serial peak expiratory flow recordings were reported to show similar patterns as in those who had OA, and the diagnosis of WEA versus OA could not be distinguished by visual inspection or by using the computerized Occupational Asthma Expert System (OASYS) [71], although the mean diurnal variability was statistically less among those who had WEA than in those who had OA [56]. Similarly, improvement in airway responsiveness to methacholine while away from work exposures compared with results during working weeks is reported as showing similar changes among those who had WEA as among those who had OA (with the diagnosis again defined by specific challenge responses) [72]. An increase in sputum eosinophils during a work period was more likely to occur among those who had OA in this study although there was overlap between groups [72]. A difficulty in using this definition of WEA to identify different characteristics of those who have OA versus WEA is the possibility that the gold standard of specific challenge may be falsely negative if the correct exposure agent is not selected or if the duration or concentration of exposure is not sufficient to induce a true response and, conversely, could be falsely positive if the exposure is irritant [73,74].

To date there are no reported studies assessing management of WEA or preventive measures. It may be expected that good pharmacologic control of asthma and limitation of exposure to asthma triggers at work may reduce morbidity and the socioeconomic impact of WEA but documentation of this is needed.
Summary

There is significant current interest not only in OA but also in the potential of work exposures to exacerbate/aggravate adult asthma. The range of potential triggers for OA and WEA is wide. OA can result in persisting asthma even after removal from exposure to the work agent and for WEA the exacerbation could range from very transient worsening of symptoms to persistent daily worsening at work. OA and WEA can have significant socioeconomic impacts. Underlying host factors, such as asthma severity and medication use, and compliance likely are contributing factors to WEA. It is hoped that epidemiologic studies in the future will help clarify these common conditions. OA is a challenge to definitively identify in epidemiologic studies. Nevertheless, case definitions for epidemiologic studies have been developed and there is a need for greater use of such tools to better identify the prevalence and causes of OA worldwide and prognostic factors and results of preventive measures.

References


Traffic, Outdoor Air Pollution, and Asthma

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It is well known that outdoor air pollution can affect the health of patients with asthma. Epidemiologic studies have shown that increased levels of outdoor pollutants are associated with acute and chronic changes in lung function, increased risk for asthma exacerbations, increased risk for work or school absenteeism, and need for rescue bronchodilators. Fortunately, we have also learned that reducing ambient levels of air pollutants can decrease acute health care use for asthma and therefore improve the quality of life of these patients [1].

The epidemiology of asthma and outdoor air pollution has shown that respiratory health effects can vary in relation to different emission sources, types of pollutants, underlying nutritional status, medication use, and genetic polymorphisms. Using sophisticated exposure assessment methods in conjunction with clinical tests and biomarkers that provide mechanistic information, the study of outdoor epidemiology and asthma has evolved into a complex multidisciplinary field. This article presents an overview of the mechanisms by which outdoor air pollution and traffic-related emissions lead to changes in respiratory health and lung function in subjects with asthma.

The outdoor air pollution mix

Polluted outdoor air contains a complex mixture of particle and gas-phase pollutants. Most epidemiologic studies on asthma and air pollution have focused on understanding the health effects of criteria air pollutants, which are routinely monitored by the Environmental Protection Agency and include ozone, nitrogen dioxide, sulfur dioxide, lead, carbon monoxide,
and particulate matter (PM) [2,3]. PM is further subdivided into coarse particulate matter or PM\textsubscript{10} (PM with an aerodynamic diameter $\leq 10 \, \mu m$), fine particulate matter or PM\textsubscript{2.5} (PM with an aerodynamic diameter $\leq 2.5 \, \mu m$), and ultrafine or PM\textsubscript{1.0} (PM with an aerodynamic diameter $\leq 1.0 \, \mu m$) [4].

The criteria pollutants are derived from different emissions sources. For example, nitrogen dioxide and ground-level ozone (which results from the effect of ultraviolet light on nitrogen dioxide) are primarily derived from vehicle exhaust, whereas sulfur dioxide derives from combustion of sulfur-containing fuels (e.g., coal burning plants). Coarse particulate matter is primarily derived from dispersed ground or fugitive dust; fine and ultrafine particulate matter comes primarily from vehicular exhaust [5]. Coarse and fine particulates differ not only in their size and physical properties, but also in their chemical composition. PM\textsubscript{10} is largely composed of geological materials, in contrast to PM\textsubscript{2.5} and PM\textsubscript{1.0}, which have larger fractions of elemental and organic carbon [6]. These PM variations in chemical composition are associated with different toxicity profiles and can be used as tracers of vehicular emissions. For example, elemental carbon can be used for tracking traffic-related emissions [7].

The first challenge in studying the impact of air pollution on asthma status is to accurately quantify exposure. Determining that a patient with asthma may be more or less susceptible to different pollutants is easy, but trying to understand the pollution mixture actually inhaled is practically impossible. Exposure to different pollution mixtures can vary by location, proximity to roads, time of day, seasonality, and other factors. Epidemiologic research on outdoor air pollution employs different methodologies to overcome many of these limitations. This may include relating health outcomes to emission sources as the main exposure of interest (e.g., proximity to roads, traffic density estimates, road densities) and use of personal air pollution monitors in smaller, better-characterized panel studies. An in-depth review of epidemiologic and exposure assessment methods used in outdoor air pollution is beyond the scope of this article. However, there are many different ways of associating air pollution exposure with respiratory health outcomes and this methodological variation is often the source inconsistent results across studies.

Outdoor air pollution and mechanisms of injury pertinent to asthma

\textit{Airway inflammation}

Outdoor air pollutants are known to exacerbate asthma by causing inflammation in the airways [8,9]. Even short-term exposures to vehicular traffic emissions (PM\textsubscript{2.5}, PM\textsubscript{1.0}, elemental carbon, and nitrogen dioxide) in subjects with asthma are associated with evidence of neutrophilic inflammation and reduced airway pH [7]. Evidence that outdoor air pollution leads to airway inflammation in asthma is also supported by studies using exhaled
nitric oxide as a biomarker. In a panel of 19 children with asthma in Seattle, a same-day increase of 10 μm/m³ of PM$_{2.5}$ was associated with increased in exhaled nitric oxide of 4.3 ppb [95% CI 1.4–7.29] [10]. Exposure to ambient elemental carbon has also been associated with increased exhaled nitric oxide, suggesting that vehicular emissions may lead to increased airway inflammation [11].

**Allergy sensitization**

Outdoor air pollution may increase the risk for asthma by mechanisms that involve increased allergic sensitization. Exposure to diesel exhaust particles (DEP) before an allergen challenge has been shown to increase Th-2 cytokine levels, when compared with allergen exposure alone. Furthermore, DEP exposure favors lymphocyte-B cell differentiation and IgE production [12,13]. Short-term ambient exposure to PM$_{2.5}$ has also been associated with increased allergic inflammation by increasing the proportion of eosinophils in the nasal lavage of asthmatic children but not in healthy controls [14]. However, large-scale epidemiologic studies, such as the European Community Respiratory Health study, did not demonstrate an association between variations of annual average regional PM$_{2.5}$ and sulfur levels and allergic sensitization [15]. In contrast, the Study on Air Pollution and Lung Diseases in Adults (SAPALDIA) found significant associations between allergic sensitization to pollen and living near streets with higher vehicular traffic [16]. Whether or not air pollution induces allergic sensitization is debatable and inconsistencies across studies may be the result of methodological differences [17].

**Clinical and physiologic lung changes associated with outdoor air pollution**

**Acute changes in lung volumes**

Subjects with asthma are far more susceptible than healthy subjects to the effects of outdoor air pollution. Most studies have found that increased concentrations of outdoor air pollution can be associated with acute reductions in forced vital capacity (FVC) and forced exhaled lung volume in one second (FEV$_1$) among persons with asthma. The magnitude and lag between exposure and change in lung function varies considerably according to the exposure assessment (type of pollutants being measured) and study design. Outdoor PM$_{10}$ and PM$_{2.5}$ have been associated with acute reductions in FEV$_1$ and FVC. These reductions in lung volumes are observed either within the same day, a few hours after exposure, or days after exposure (lag response) [7,18].

Sulfur dioxide is oxidized in the atmosphere to sulfuric acid with resulting acid aerosol and acid rain production. Acid aerosols are associated with significant reductions in FEV$_1$ and FVC. Sulfur dioxide can acutely induce bronchoconstriction in subjects with asthma [19,20]. Moreover, ozone is
a strong oxidizing agent well known to reversibly reduce FEV$_1$ and FVC, promote bronchial hyperresponsiveness, increase airway resistance, and reduce peak expiratory flows [21,22].

 Compared to subjects without chronic airway obstruction, subjects with asthma exhibit larger reductions in FEV$_1$ in association with exposure to ambient nitrogen dioxide [23]. In controlled exposure chamber studies, however, investigators have failed to show FEV$_1$ reductions in asthmatics exposed to nitrogen dioxide [24]. Discrepancies between chamber exposure and epidemiologic studies are not uncommon and may derive from the fact that, in an epidemiologic study, what we attribute to be the exposure of interest functions as a tracer or surrogate for other pollutants or a complex mixture of pollutants, such as a mixture of nitrogen dioxide, PM$_{2.5}$, and other vehicular traffic–related emissions.

**Chronic lung-volume changes**

Understanding the chronic respiratory health effects of outdoor air pollutants is more complex. It requires either a longitudinal approach in large study populations with repeated measures of lung function and air pollution exposure over time, or an ecological approach in which lung function values are compared in populations across a gradient of outdoor air pollution levels. The Children’s Health Study is a large cohort study that enrolled children from 12 communities with varying air pollution exposure profiles across California. Results from this cohort show that children from ages 10 to 18 years exposed to higher air pollutant concentrations have reduced lung growth. Deficits in lung function were associated with nitrogen dioxide, acid vapor, and PM$_{2.5}$, but not with ozone [25]. Importantly, air pollution–related lung-growth deficits occurred in children with and without asthma. In a dynamic cohort from Mexico City that included 3120 healthy children 8 years of age at baseline and followed for 3 years, exposure to ozone, PM$_{10}$, and nitrogen dioxide were associated with significant deficits in lung growth [26]. Results from these studies suggest that air pollution–related deficits in lung growth prevents many children from achieving their peak lung volume.

Chronic exposure to outdoor air pollutants is also associated with increased rate of lung-volume decline over time. Results from the SAPALDIA show that long-term exposure to pollutants (nitrogen dioxide, PM$_{10}$, and sulfur dioxide) is associated with increased decline in FEV$_1$ and FVC. For FVC, an increment of 10 μg/m$^3$ in PM$_{10}$ was associated with a 3.4% change in FVC [27]. The good news is that lung function can improve once exposure to air pollution is reduced, even after long-term exposure. In the same study, 9651 adults (18 to 60 years of age and assessed in 1991 and 2002), experienced an overall reduction in their outdoor PM$_{10}$ exposure. The net effect of a decline of 10 μg of PM$_{10}$ per cubic meter over an 11-year period was to reduce the annual rate of decline in FEV$_1$ by 9% and of FEF$_{25–75}$ by 16% [28]. In the California Children’s Study, participants who moved to
communities with lower PM$_{10}$ showed increased lung growth, whereas moving to higher PM$_{10}$ environments was associated with reduced lung growth. These associations were predominantly observed in children who had been living in their new communities for at least 3 years [29].

Outdoor air pollution and asthma health status

Many epidemiologic studies have shown that increased outdoor air pollutant levels are a significant morbidity risk for subjects with asthma. Increased outdoor exposure to air pollution has been associated with increased severity of respiratory symptoms, increased risk for asthma exacerbations requiring emergency department evaluation or hospitalization, and more frequent urgent medical visits and use of asthma medications [2,4,30]. Also, higher levels of air pollution are associated with increased school and work absenteeism resulting in a large economic cost to society [31,32].

Clearly not every subject with asthma experiences adverse respiratory outcomes when exposed to higher levels of outdoor air pollutants. Several factors have been shown to either increase susceptibility or confer resistance to air pollution. The interaction between environment and genetic polymorphisms is an area of intense research and some recent studies are worth reviewing.

In asthmatics, the presence of GSTM1 (glutathione $s$-transferase null polymorphism) and GSTP1 (val/val genotype) has been associated with increased susceptibility to ambient ozone exposure [33,34]. The GSTM1 polymorphism, which is present in approximately 40% of the general population, has been associated with increased levels of nasal biomarkers of inflammation and reduced peak expiratory flows in asthmatic children in association with ozone [33]. Both GSTM1 and GSTP1 polymorphisms are also associated with increased dyspnea in children with asthma exposed to ozone [33]. The presence of GSTM1 also increases the risk for systemic inflammation in association with traffic-related particles (black carbon and concentration of particles) [35]. Children who are GSTM1 homozygous and most susceptible to outdoor air pollution benefit the most from antioxidant supplementation. Romieu and colleagues [34] showed that, compared with placebo, children receiving antioxidant supplementation did not exhibit ozone-related reductions in lung volumes. Antioxidant supplementation was most effective in protecting children who were GSTM1 null homozygous.

Not all genetic polymorphisms have been associated with increased susceptibility. Among 3699 children participating in the children’s health study in California, those who were homozygous for the tumor necrosis factor $\alpha$ (TNF-$\alpha$) 308G polymorphism (range from 71% non-Hispanic whites to 87% in Asians) had a reduced risk for lifetime asthma prevalence and wheezing, compared with those carrying one allele. Furthermore, homozygous children living in lower-ozone communities were protected from...
wheezing in relation to ozone exposure, particularly in those with the GSTM1 polymorphism [36]. It is thought that the homozygous TNF-α 308G polymorphism may protect from ozone exposure by reducing the inflammatory response to oxidative stress [36].

**Air pollution as a risk factor for asthma incidence**

Outdoor air pollution not only exacerbates asthma, but is also a risk factor for developing new-onset asthma. For example, increased asthma incidence has been described in children playing outdoor sports exposed to higher ozone levels. In this study, children who played three or more outdoor sports in communities with high ozone concentrations during the summer had a relative risk of developing asthma of 3.3 [95% CI 1.9–5.8], compared with children playing no sports. Also, the risk for asthma prevalence increases proportionately with increased vehicular emission exposures, suggesting that chronic exposure to these pollutants may increase the risk of developing asthma [37,38]. In a large study of 6000 children from six French cities, the 3-year averaged concentration of ozone, PM_{10}, sulfur dioxide, and nitrogen dioxide were associated with increased odds of developing allergic rhinitis, atopy (positive skin test), and lifetime asthma [39]. A matched case control study by Zmirou and colleagues evaluated the risk for incident asthma (recent medical diagnosis within the preceding 2 years) in children of ages between 4 and 14 years and exposure to traffic density. Exposure to traffic density was calculated retrospectively and divided into an overall cumulative life exposure and an early life exposure (birth to 3 years). Early life exposure to traffic density, but not the cumulative measure, was associated with increased odds for asthma incidence [40]. Results from these studies suggest that outdoor air pollutants may play a role in increasing the risk for developing asthma and atopy, particularly early in life.

**Reducing the health burden associated with outdoor air pollution**

Relocating to cities with less air pollution can reduce the risk for some of the chronic lung effects and improve respiratory health. However, this option is probably not feasible or practical for most patients with asthma. Health care providers should advise their patients with asthma to follow their local air pollution forecasts to avoid outdoor exposure as much as possible during alerts. This means cutting out exercise during peak air pollution hours [41]. This advice is useful for reducing ozone exposure in subjects who live or work in air-conditioned environments. Outdoor avoidance may not provide the same degree of protection from fine and ultrafine particles, which have higher filtration coefficients and can achieve relatively high concentrations indoors.

Whether treatment with inhaled corticosteroids or other antiasthma medications can provide relief from air pollution is unclear. In a panel of 19 children with asthma, exposure to ambient PM_{2.5} was associated with increased
exhaled nitric oxide. This association was not observed in children taking inhaled corticosteroids (change in exhaled nitric oxide per 10 μg/m³ increase in PM$_{2.5}$ in children with inhaled corticosteroids: 6.3 [95% CI 2.6–10]; change in exhaled nitric oxide per 10 μg/m³ increase in PM$_{2.5}$ in children not on inhaled corticosteroids: –0.77 [95% CI -4.6, 3]) [42]. In the California Children’s Health Study, ambient ozone exposure was associated with increased prevalence of medication use and wheezing among asthmatic children, particularly in those who spent more time outdoors [43]. However, the prevalence of medication use in this study was a proxy for increased susceptibility to the exposure and no data was provided to determine whether use of inhaled corticosteroids modified the association with outdoor air pollutants. Rundell and colleagues showed that one dose of montelukast prevented bronchoconstriction in young males exercising during exposure to high PM concentrations [44]. This suggests that particulate air pollution could induce lung function deficits via leukotriene inflammatory pathways. Two other small exposure studies have shown that long-acting theophylline and salmeterol may prevent sulfur dioxide–mediated bronchoconstriction [45,46]. These results clearly need to be replicated in a larger study population. The use of antioxidant supplementation has been shown to reduce the impact of outdoor air pollution on respiratory symptoms and decline in lung volumes [34]. However, these results stem from small panel studies and do not provide the level of evidence needed to make broader clinical or public health recommendations to use antioxidants as a secondary prevention strategy.

Traffic and asthma

Asthma and traffic-related emissions

Evidence that there is considerable spatial variability in the concentration of traffic-related pollutants has sparked interest in assessing the health effects associated with vehicular emissions. Several studies have found that exposure to traffic-related emissions are associated with higher rates of adverse respiratory health outcomes in comparison with background air pollution exposure [47–51]. This phenomenon may be explained by the pollutant mix properties near vehicular emission sources, including larger concentration of fine and ultrafine particles [52] and higher concentrations of carbon monoxide and nitrogen dioxide levels [53]. Although there is no clear consensus on what constitutes exposure to vehicular-related emissions, most studies have found that the rate of adverse respiratory health effects appears to increase proportionately in relation to road-proximity [38] and with increasing traffic density [54]. Proximity to major traffic roads and high traffic density has been associated with higher rates of wheezing [50], atopy [55,56], respiratory symptoms, and health care use in children [57–59].

In a cohort of 200 children aged 6 to 12 years (half of them with asthma), the author and colleagues determined the associations between road
densities (defined as total kilometers of roads within a defined area) near schools and homes and exposure to outdoor air pollution (nitrogen dioxide, elemental carbon, and PM$_{2.5}$). These exposures were then related to changes in lung volumes and exhaled nitric oxide. This study found that road density (a proxy measure for vehicular traffic) within the 50- and 100-m buffers (radius around a geographically designated area), particularly at home, was associated with reduced FEV$_1$ and FVC and increased exhaled nitric oxide only in children with asthma [60]. Because road density and related traffic volumes remain constant or change slowly, road density constitutes a persistent traffic exposure. In contrast, no significant associations with the ambient levels of measured pollutants (a longitudinal exposure) were observed. One possibility to explain this finding is the potential for exposure misclassification. For example, the study's pollutant exposure assessment may not accurately represent exposure during a critical time window that would be associated with changes in exhaled nitric oxide or lung volumes. Alternatively, cumulative long-term exposure may be more relevant than shorter-term peak exposures to pulmonary function in this cohort.

The effect of exposure to traffic-related emissions on respiratory health, above and beyond the background air pollution, remains controversial. Other studies have not shown significant associations [61–63]. Discrepancies among studies can be partly explained by different exposure measures, including subjective quantification of traffic density, direct measurement of traffic counts, and exposure defined at different proximity levels to roads with greater traffic densities. Also, an important source of bias when evaluating the effects of vehicular emissions is socioeconomic status position (SEP). Lower SEP has been associated with road proximity and with increased vulnerability to the effects of air pollutants [64]. Disentangling the extent of bias attributed to SEP in traffic studies can be quite difficult, as the SEP definition among studies was highly variable. Additionally, other unmeasured factors, such as noise and related stress, can be important sources of bias [65,66].

Summary

There is growing evidence that exposure to traffic-related emissions is different than that of background air pollutants in terms of the composition of the pollution mix and the health risks. However, given the broad differences in methodology and exposure assessment, it is difficult to reach a consensus on what constitutes an exposure to “traffic- or vehicle-related emission.” This limitation leaves many important questions unanswered and hampers the capacity of research to translate results into community environmental improvements aimed at reducing health risks. For example, there is no consensus regarding exposure thresholds. That is, at what distance from roads or traffic emission sources would the exposure to vehicular emissions be diminished to safe levels? Should we advise patients with asthma to avoid prolonged exposure in close proximity to roads? If so, how much time...
constitutes prolonged exposure? What distance is far enough away? What volume of traffic is tolerable? Should an asthmatic be advised not to reside or attend school or work based on the potential for nearby traffic exposure? The answers to these questions could have clinical implications for the caring of patients with asthma and for public health policies, urban planning and development, and other areas of society.

References


Obesity and Asthma
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Over the last two decades, the convergence of secular trends indicating increases in the prevalence of obesity and asthma has led to a hypothesis that these two disorders might be related. Data from the 1999–2002 National Health and Nutrition Examination Survey (NHANES) indicate that 65% of U.S. adults greater than 20 years of age are overweight or obese [1], a 10% increase when compared with the 1988 through 1994 period [2]. Although asthma affects a smaller proportion of the U.S. population than does obesity and recent data suggest asthma prevalence may not be increasing as rapidly as in the past, the age-adjusted asthma prevalence of 7.9% reported based on 2005 National Health Interview Survey data [3] is more than twice that reported in 1984–1986 National Ambulatory Medical Care Survey data [4].

Although the mechanisms underlying a putative relationship between obesity and asthma have not been fully described, a relatively mature body of literature suggests that obesity increases the risk of incident asthma [5]. Obesity may also skew prevalent asthma toward a more difficult-to-control phenotype [6] and alter response to therapy [7,8]. Despite these emerging data, much remains to be elucidated [9], leading some to question whether the two disorders are related [10]. This review addresses studies that could be interpreted as supporting the hypothesis that obesity leads to asthma. We evaluate animal studies that provide biological underpinnings to an association between the two disorders and clinical and epidemiologic studies that suggest that the relationship between these two disorders is clinically important.

Obesity and asthma incidence and prevalence

Cross-sectional and case-control studies in children and adults have demonstrated an increased prevalence of asthma in obese individuals [11–19].

Support: NIH HL090982.
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doi:10.1016/j.iac.2008.03.003
Representative of these studies is the study by Sin and colleagues [18], who used data from 16,692 participants (age ≥ 17 years) in the Third National Health and Nutrition Evaluation Survey (NHANES III). The investigators categorized body mass index (BMI, defined as kg/m²) into quintiles and evaluated the relationship between BMI quintile and self-reported asthma, degree of airflow limitation, and rescue bronchodilator use. In their analysis, individuals in the highest BMI quintile had the greatest odds of self-reported asthma (odds ratio [OR], 1.50; 95% confidence interval [CI], 1.24–1.81). There was a trend for increasing odds of asthma as BMI increased (P = .001 for the trend), with similar findings of increased rescue bronchodilator use as BMI increased. These clinical outcomes were not associated with a similar trend toward increasing airflow limitation as BMI increased. Beckett and colleagues [11] used data from 4547 participants in the Coronary Artery Risk Development in Young Adults study of 18- to 30-year-old subjects. In this analysis, there was no association between increasing baseline BMI quintile and baseline asthma prevalence (P = .74 for difference between quintiles), but elevated BMI at baseline was associated with an increased subsequent risk of developing asthma, with a hazard rate ratio of 1.6 (95% CI, 1.12–2.30) in the highest BMI quintile compared with the reference quintile.

Many of these cross-sectional and case-control studies benefit from the ability to evaluate large numbers of subjects and have provided important insights into the epidemiology of the two disorders. A potential limitation of studies of thousands of subjects is a limited capacity to carefully phenotype participants with regard to the exposure and outcome variables, and many of these studies relied on self-reported weight and height to determine BMI or self-reported asthma diagnosis to ascertain cases of asthma, raising the possibility of inaccuracies or biases related to reporting. This limitation does not apply to all epidemiologic studies of the obesity–asthma relationship, however, and in studies that used measured rather than self-reported height and weight to define BMI [11,14,17] there was a significant association between elevated BMI and asthma. Perhaps more limiting with regard to the generalizability of many of these studies is the use of a self-reported physician’s diagnosis of asthma rather than formal physiologic evaluation to determine cases, particularly because respiratory symptoms classified as asthma could be dyspnea due to obesity-related physiologic impairment [20,21].

Prospective studies have often included more rigorous definitions of asthma in their study populations [22–28] and as a group introduce the additional benefit of being able to assess whether pre-existing obesity is associated with a subsequent increase in asthma risk. Most have shown a steady dose–response relationship with an elevation in incident asthma as BMI increases, and most demonstrate the effect to be stronger in women than in men. Many of these longitudinal studies control for diet and physical activity, strengthening the conclusion that it is obesity,
and not a lack of exercise or a dietary factor, that is associated with asthma. For example, Camargo and colleagues [22] performed a prospective analysis of the relationship between BMI and asthma in a study of 85,911 women followed for 4 years. In their multivariate model, the relative risk of incident asthma increased as BMI across six categories, with relative risks ranging from 0.9 (lowest BMI group) to 2.7 (highest BMI group; \( P \) value for trend < .001). This study differed from some other prospective studies in its enrollment of women only and in the use of self-reported height and weight, but other prospective studies by Ford [24] and Nystad and colleagues [27], which included men and women and used a definition of BMI that was based on measured weight and height, found associations between elevated BMI and incident asthma of similar strength.

Some of these prospective studies have suggested that the relationship between obesity and asthma is stronger in women, leading to the hypothesis that this effect may be modified by estrogen or another sex-based biologic difference. However, the difference in the point estimates of effect between men and women is usually small, and some studies have shown conflicting results. For example, in Chen and colleagues’ [23] 2002 Canadian National Population Health Survey study, the incidence of asthma was associated with the degree of baseline adiposity in women but not in men, but two other prospective studies [25,29] demonstrated that the association between obesity and asthma was similar in men and women. In children, Castro-Rodríguez and colleagues [30] showed that although there was no association between BMI and asthma at age 6, the development of overweight or obesity between age 6 and 11 was associated with a sevenfold increased risk of new asthma symptoms, and the effect was strongest among girls beginning puberty before age 11. Finally, in adult postmenopausal women, exogenous estrogen in the form of hormone replacement therapy has been associated with an increased risk of asthma [31], and a recent study showed that the association between BMI and asthma severity was stronger in women with early menarche than in women without early menarche [32]. Although potential mechanisms underlying an association between sex hormones and asthma are being explored [33–36], the importance of these models in the obesity–asthma relationship in humans remains to be determined.

The majority of prospective studies have reported that obesity is a risk factor for the development of a new diagnosis of asthma, with risk or odds ratios of between 1.1 and 3.0 comparing the highest with lowest BMI categories, with the suggestion of a stronger effect in women. When this heterogeneity of effect was examined in a meta-analysis of studies investigating overweight and obesity as a risk factor for incident asthma, the authors concluded that, overall, overweight and obesity increased the odds of incident asthma in a dose-dependent manner and that the strength of this relationship was similar in men and women. Random-effects meta-analysis
of data from seven studies (n = 333,102) indicated that, compared with normal weight, overweight and obesity were associated with an increased odds of incident asthma (OR, 1.51; 95% CI, 1.27–1.80). A dose–response effect of elevated BMI on asthma risk was observed; the OR for incident asthma comparing normal weight versus overweight (BMI 25–29.9) was 1.38 (95% CI, 1.17–1.62) versus 1.92 (95% CI, 1.43–2.59) comparing normal weight with obesity (BMI ≥ 30), with P < .0001 for the trend. A similar increase in the odds of incident asthma due to overweight and obesity was observed in men (OR, 1.46; 95% CI, 1.05–2.02) and women (OR, 1.68; 95% CI, 1.45–1.94) [5]. Some studies call the strength of obesity as an asthma risk. For example, in the community-based cohort study of Hasler and colleagues [37], which followed 591 adults between the ages of 20 and 40, asthma was significantly associated with obesity cross sectionally (OR, 3.9; 95% CI, 1.2–12.2), but a multivariate analysis revealed that obesity was not a risk factor for subsequent asthma; rather, asthma was a risk factor for subsequent obesity.

The pediatric literature also suggests a relationship between body mass and asthma risk with regard to asthma and atopy, a principal asthma risk factor in children. For example, in a prospective study of 9828 children age 6 to 14 who were followed for a median of 5 years, Gold and colleagues [38] reported that for girls, higher BMI at entry and a greater increase in BMI over the study were associated with a higher risk of asthma, with a 2.2 times greater risk of asthma in the highest versus lowest BMI quintile in girls. In boys and girls enrolled in the study, greater increases in BMI over the course of the study were associated with an elevated risk of asthma. A report from the Children’s Health Study echoed the dose-dependence of increased BMI and asthma risk, with overweight (BMI 25–29.9) and obesity (BMI ≥ 30) increasing the risk of incident asthma (OR, 1.52; 95% CI, 1.14–2.03 and OR, 1.60; 95% CI, 1.08–2.36, respectively), with obese boys having an increased risk of asthma compared with girls [39]. As in adults, not all studies of children show a significant association between obesity and asthma. Chinn and Rona [40] reported that in a group of British school children, the annualized odds of developing asthma was 1.09 (95% CI, 1.07–1.11) for boys and girls, a number that did not change significantly when adjusting for BMI.

The relationship between obesity and atopy in children seems to be less robust than the relationship between obesity and asthma, as evidenced by data from pediatric participants in NHANES III. In unadjusted analyses, the prevalence of asthma and atopy increased with increasing BMI, but after adjusting for confounding factors, only the relationship between BMI and asthma remained significant (OR, 1.77; 95% CI, 1.44–2.19) [41]. In a study from Hancox and colleagues [42], elevated BMI was modestly but significantly (OR, 1.14; 95% CI, 1.10–1.30) associated with positive skin tests and elevated IgE; this relationship was not seen in boys.
Obesity and asthma severity

Compared with large-scale epidemiologic studies, there have been fewer reports of the effect of elevated body mass on biomarkers of asthma impairment and risk in well-characterized study populations. Although studies have suggested that health status is impaired in obese individuals with asthma [43], it is not clear if this due to increased airway inflammation, altered pulmonary physiology, or other variables that could influence health status. In children, a report from the Childhood Asthma Management Program suggested that there was no statistically significant relationship between BMI and many markers of asthma control, including school absenteeism, emergency department care, requirement for corticosteroids, or hospitalizations. BMI did not seem to affect eosinophil counts or IgE concentrations, and although there was a weak inverse relationship between BMI and bronchodilator reversibility ($\beta = -0.003; P = .02$), there was no impact of BMI on airway hyperresponsiveness (AHR) to methacholine [44]. The generalizability of these data is somewhat limited by the observation that most participants were pre-pubertal and that the median BMI was 17.09. A recent study by Santamaria and colleagues [45] evaluated a population more obese (50 children with a $BMI > 95th$ percentile) than that in CAMP, and although there was a high prevalence of atopy (58%) in the study population, significant differences were not found between lean and obese participants with regard to exhaled nitric oxide (FeNO) concentrations (a biomarker of airway inflammation) independent of and adjusted for the diagnosis of atopy or asthma.

There are conflicting data about whether obesity makes prevalent asthma severe. The observation that obesity is associated with a more severe asthma phenotype has been supported in part by data from the TENOR study of patients who have severe asthma, in which the mean BMI in adults with severe asthma was 30.4 kg/m² [6]. However, a recent report from the Severe Asthma Research Program investigators [46] indicated that obesity was not more prevalent in severe [47] than in moderate asthma, raising some uncertainty about the importance of obesity as a modifier of asthma severity. This clinical controversy has perhaps been further underscored by recent studies that fail to demonstrate a robust relationship between obesity and biomarkers of airway inflammation in adults who have asthma. In an evaluation of lung function and spirometry in 297 patients who had asthma across the BMI spectrum, there was an inverse relationship between BMI and FeNO in unadjusted analyses ($r_S = -0.307; P < .001$) and in analyses adjusted for age, forced expiratory volume in 1 second (FEV₁), sex, concurrent atopy, and inhaled corticosteroid use [48]. McLachlan and colleagues [49] reported similar findings in a population-based cohort of approximately 1000 individuals, demonstrating that although adiposity (reflected in percentage of body fat) was associated with asthma and airflow limitation in women, there was no meaningful association between FeNO or adiposity
in women or men. Todd and colleagues [50] used induced sputum cell counts as an alternative means of assessing airway inflammation in 727 obese subjects with and without asthma. Although sputum eosinophil counts were higher overall in subjects who had asthma, there was no significant correlation between BMI and sputum eosinophils in participants who had asthma or in the study population as a whole.

Although these data are not conclusive, in aggregate they seem to suggest that biomarkers of airway inflammation do not necessarily increase as body mass increases in subjects who have asthma.

**Obesity and pulmonary physiology**

Obesity has well-described effects on lung function, with physiologic studies suggesting that obesity has important mechanical effects that can lead to symptoms of dyspnea without causing the pathophysiologic changes commonly observed in asthma. Alterations in airflows, respiratory system compliance, lung volumes, peripheral airway diameter, and AHR have been described in obesity.

Obesity causes airflow limitation, with reduction of FEV$_1$ and forced vital capacity (FVC) [51]. Unlike asthma, these reductions in airflow are typically symmetric and result in a preserved FEV$_1$/FVC ratio [18]. Some authors have shown that the FEV$_1$/FVC ratio is increased in obesity, consistent with a restrictive physiology [51]. Reductions in absolute airflows are accompanied by a reduction in respiratory system compliance due to a combination of excess soft tissue weight compressing the thoracic cage, fatty infiltration of the chest wall, and increased pulmonary blood volume [52–55]. These alterations of pulmonary physiology lead obese individuals to breathe shallowly near their closing volume [56], which may be one cause of the observed subjective increase in dyspnea [18]. Lung volumes, particularly the expiratory reserve volume and functional residual capacity (FRC) [51,57], are also reduced in obesity.

The reductions in lung volumes observed in obese individuals are associated with a reduction in peripheral airway diameter [58], a phenomenon that over time perturbs smooth muscle function, potentially increasing airway obstruction and AHR [59]. The available clinical data on obesity and AHR are conflicting. In the European Community Respiratory Health Survey, AHR increased with increasing BMI in men but not in women [60], and in a case-control study from participants in the Normative Aging Study, high initial BMI was associated with the development of AHR to methacholine (OR, 10; 95% CI, 2.6–37.9) when subjects in the highest BMI quintile were compared with those in the middle BMI quintile. There was also a linear relationship between increasing BMI over the study period and the subsequent development of AHR [61].

In contrast, Schachter and colleagues [62] showed that in a group of 1971 adults, BMI was associated with a diagnosis of asthma and symptoms of
dyspnea and wheeze but was not associated with airflow obstruction or AHR. Another study from this group showed that elevated BMI was a risk factor for wheeze and cough but not AHR or the diagnosis of asthma in a study population of almost 6000 children [63]. Therefore, although obesity leads to a number of physiologic perturbations that could cause respiratory symptoms, physiologic studies do not uniformly support the conclusion that obesity leads to increases in AHR.

Medical weight loss studies in patients who have asthma have demonstrated that weight loss can lead to improvements in clinical and physiologic parameters. In an observational study of 14 obese patients who had asthma before and after an 8-week very-low-calorie diet, weight loss reduced diurnal peak flow variability, increased FRC, and improved measures of airflow limitation [64]. In a similarly designed, 6-month medical weight loss study of 58 obese women (24 of whom had asthma), weight loss improved lung function as measured by FEV$_1$ and FVC but did not affect methacholine responsiveness [65]. In a study of two groups of 19 patients who had obesity and asthma, the group randomized to supervised medical weight loss demonstrated improved lung function, asthma symptoms, and health status when compared with control subjects [66]. In a more substantial clinical weight-loss setting, studies of patients undergoing surgical weight-loss operations have demonstrated substantial improvements in physiologic parameters such as expiratory reserve volume and FRC, along with improvements in total lung capacity, residual volume [67], and respiratory muscle function [68].

**Systemic and airway inflammation in obesity**

In a subset of obese individuals, obesity is associated with a systemic pro-inflammatory state [69], which has been implicated in a number of the metabolic and cardiovascular complications of obesity. Whether this environment can lead to the development of airway inflammation and asthma in humans is not known, but a number of observations suggest that obesity might affect the lung by modulating airway inflammation.

Much of the literature focusing on the relationship between obesity, airway inflammation, and asthma has focused on the role of leptin. Leptin, the product of the $Ob$ gene, is a central mediator of inflammation in obesity and has been shown to regulate T-cell proliferation and activation, to recruit and activate monocytes and macrophages, and to promote angiogenesis [70]. Leptin is also important for normal lung development, serving as a critical mediator of the differentiation of lipofibroblasts to normal fibroblasts and of pulmonary surfactant phospholipid synthesis [71].

Exogenous leptin has been shown to modulate allergic airway responses in mice, independent of obesity. Shore and colleagues [72] sensitized and challenged lean BALB/cJ mice with ovalbumin and infused saline or leptin subcutaneously. Leptin infusion led to increased serum leptin levels and was
associated with an enhancement of AHR and an increase in serum IgE after inhaled ovalbumin challenge, responses not observed in animals challenged with inhaled phosphate-buffered saline. There was no effect of leptin administration on bronchoalveolar lavage (BAL) fluid cell counts or lung tissue cytokine mRNA expression. Endogenous leptin levels can be increased by overfeeding wild-type lean mice, leading to obesity and enhancing the airway inflammatory response. Overfed mice that were sensitized and challenged with ovalbumin had higher antigen-induced T-cell responses, increased mitogen-induced splenocyte interferon-γ production, and increased numbers of tracheal mast cells compared with lean control mice, although ovalbumin-specific immunoglobulin levels were reduced in obese mice versus lean control mice [73]. These studies suggest that leptin seems to have an important immunomodulatory role that is relevant to airway function and immune response, independent of body mass.

The relationship between obesity and enhanced airway inflammation cannot be attributed solely to leptin because the obese leptin-deficient ob/ob mouse demonstrates enhanced airway immune response. In a study of airway response to ozone, Shore and colleagues [74] exposed lean wild-type C57BL/6J mice and obese ob/ob mice to ozone, after which AHR and airway inflammation were evaluated. Exposed ob/ob mice had enhanced AHR when compared with lean control mice, and although BAL levels of eotaxin (an eosinophil chemoattractant) were increased, a predominantly Th1 inflammatory phenotypic response was observed in the ob/ob mouse, with elevated BAL levels of interleukin (IL)-6 and the neutrophil chemoattractants MIP-2 and KC. In this study, a subset of lean and obese mice was given intraperitoneal injections of leptin before and directly after ozone exposure, and although leptin administration did not further enhance inflammatory responses in the ob/ob mouse, leptin significantly increased BAL levels of IL-6 and KC in lean control mice. This suggests that the mechanisms by which exogenous leptin alters airway immune response might vary between obese and lean animals, depending on factors such as endogenous leptin concentrations, receptor number or affinity, or other concurrent modifications of inflammatory pathways.

A recent set of experiments from Johnston and colleagues [75] evaluated AHR and other relevant biomarkers of airway inflammation after ovalbumin sensitization and challenge in wild-type (lean) mice, ob/ob mice, and db/db mice (deficient in the leptin receptor but with normal leptin concentrations). Innate AHR was increased in ob/ob mice when compared with wild-type mice, and ovalbumin sensitization and challenge further enhanced AHR in ob/ob mice and induced a nearly twofold greater increase in serum IgE in ob/ob mice than that observed in wild-type mice. Although AHR and serum IgE were increased in the obese mice when compared with lean wild-type control mice, commensurate increases in eosinophil counts and Th2 cytokine expression were not observed; in fact, lower levels of these biomarkers were seen in the obese mice. The authors concluded that although
allergic sensitization increased pulmonary resistance and serum IgE, these alterations could not be attributed to the induction of a Th2 inflammatory profile in the airway.

**Obesity as a modifier of therapeutic response in asthma**

In obesity, systemic inflammation [69] may not only increase asthma risk but may also interfere with response to controller therapies, particularly inhaled corticosteroids. Many of the cytokines and other mediators found to be elevated in obesity-related systemic inflammation (e.g., leptin, tumor necrosis factor [TNF]-α, IL-6, and C-reactive protein) have been reported to mediate the development of glucocorticoid (GC) resistance in asthma [76]. Emerging clinical data suggest that there is the potential for an interrelationship between obesity-related systemic inflammation and glucocorticoid resistance because TNF-α and IL-6 have been reported to be up-regulated in lung macrophages from patients who had glucocorticoid-resistant asthma [77], suggesting that the cytokine environment described in obesity may modify therapeutic response to GCs. In this regard, two recent reports [7,8] indicate that overweight and obese patients who have asthma may not respond as well as their lean counterparts to inhaled GCs, the most effective asthma controller therapy [78,79]. Peters-Golden and colleagues [8], in a post hoc analysis of clinical trials randomizing subjects to beclomethasone, montelukast, or placebo, reported that clinical response to beclomethasone (as reflected by asthma control days, a composite of rescue β-agonist use, nighttime awakenings, and concurrent asthma exacerbation) was reduced as BMI increased, a trend not observed with montelukast. Significant differences with regard to lung function (measured as FEV1) and rescue β-agonist use were not demonstrated, and in all BMI strata there was a numerically greater response to beclomethasone than to montelukast versus placebo, although these differences did not achieve statistical significance in overweight and obese participants. A separate post hoc analysis by Boulet and Franssen [7] also demonstrated a reduction in asthma control achieved in response to fluticasone as BMI increased; their pooled analysis of 1242 patients who had asthma allocated to fluticasone (100 μg twice daily) or fluticasone/salmeterol (100 μg/50 μg twice daily) suggested that, with both forms of asthma controller therapy, obese patients who had asthma were less likely to achieve asthma control than were those who were not obese.

The elevations in TNF-α observed in obesity may be relevant to the treatment of obese patients who have asthma. A recent clinical trial demonstrated that increased expression of membrane-bound TNF-α, TNF-α receptor 1, and TNF-α–converting enzyme in peripheral blood mononuclear cells from patients who had severe asthma were associated with GC insensitivity [47]. This study also suggested a beneficial effect of soluble TNF-α receptor etanercept in these patients, as shown by improvements in AHR, FEV1, and
asthma-related quality of life [80], raising the possibility that controller agents other than corticosteroids may be effective in obese patients who have asthma in whom systemic inflammation and GC insensitivity are shown to be important factors.

Summary

Although emerging data are beginning to shed light on the nature of the obesity–asthma relationship, much work remains to be done. Longitudinal epidemiologic investigations suggest that there is an association between the two disorders, with obesity increasing an individual’s risk of developing asthma. In studies of carefully phenotyped prevalent asthma, the impact of BMI on asthma status seems to be modest. Careful phenotyping studies in matched cohorts of subjects with and without asthma and obesity are needed to describe how airway physiologic and inflammatory phenotypes are modified by obesity. Although animal models have the potential to expand our understanding, a continued emphasis on well-characterized animal models with regard to the interaction of obesity, environmental exposures (eg, allergen, infection), genetics, host factors (eg, sex hormones), and airway inflammation is needed to guide further hypothesis development and testing in humans. Clinical investigators should conduct studies to identify the most appropriate interventions and outcomes with which to optimize care for this important subset of patients who have asthma.

References


Chinn S, Jarvis D, Burney P. Relation of bronchial responsiveness to body mass index in the ECRHS. European Community Respiratory Health Survey. Thorax 2002;57:1028–33.


Dietary Factors and the Development of Asthma

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Asthma and related allergic diseases are substantial public health problems worldwide [1,2]. Data from the United States Centers for Disease Control indicate that the self-reported prevalence of asthma in the United States increased 73.9% from 1980 to 1996 [1]. In 2002, estimates from the National Health Interview Survey revealed that 72 people per 1000, or 20 million people, have asthma in the United States [3]. Worldwide, it is clear that more affluent westernized countries and countries making the transition to a westernized lifestyle have higher prevalence of asthma compared with less developed countries [2]. Although recent findings suggest that the prevalence of asthma may have reached a “plateau” in most industrialized countries [4–8], there are no clear reasons for the increase in prevalence of asthma and allergies in these developed countries. It is likely that a changing environment and the behaviors associated with a “westernized” lifestyle are contributing to the problem. It is postulated, for example, that, because of improvements in hygiene and control of infectious disease, decreased exposure to infectious agents in early childhood may predispose to the development of asthma and allergies [9]. Thus, some studies have shown that exposure to markers associated with such infectious agents as endotoxin [10], farm animals [11], and pets [12] may decrease the risk of these disorders. Other factors associated with a western lifestyle and implicated in the development of these conditions include obesity [13] and exposure to allergens [14]. Another aspect of this lifestyle is the change in diet that has occurred. This article briefly discusses this change, describes how diet is evaluated in epidemiologic studies, and summarizes existing data relating...
diet with asthma. There have been a number of comprehensive reviews of this topic [15–17]. This article updates these with recent studies, where available. Additionally, in the past 5 years, new information has surfaced regarding the association of early-life diet and nutrition on subsequent asthma [18,19]. This article reviews these studies, with an emphasis on effects of maternal diet in pregnancy.

**Dietary changes in westernized countries**

In 1994, Seaton and colleagues highlighted changes in the United Kingdom diet that had preceded and paralleled the increase in asthma and atopic disease [19,20]. They observed that there had been a decrease in vegetable consumption, particularly of potatoes and green vegetables, and suggested that a westernized diet, increasingly deficient in antioxidants, had increased population susceptibility with consequent large increases in the prevalence of asthma and allergy. In the United States, recent analyses have shown that fruit and vegetable consumption remains low [21,22] despite public health efforts to improve overall diet quality [23]. It is postulated that decreased dietary antioxidant intake leads to reduced antioxidant defenses in the lung, leading to increased oxidative stress with increased susceptibility to airway inflammation and asthma [24].

Aside from antioxidants, intake of fats, particularly the changing composition of polyunsaturated fatty acids (PUFAs) in western diets, has been implicated in asthma. In 1997, Black and Sharpe [25] reviewed the changes in dietary intake of fats as a result of public health efforts to reduce the incidence of coronary heart disease, and suggested that the changing composition of PUFAs played a role in the increase in asthma and allergies. In westernized countries, including the United States, the reduction in intake of saturated fat was accompanied by an increase in consumption of n6 PUFAs, particularly linoleic acid and arachidonic acid, through increased use of margarine and vegetable oils (instead of butter and lard) [26,27]. In addition, there has also been a decrease in consumption of oily fish, a rich source of n3 PUFAs, such as eicosapentaenoic acid and docosahexaenoic acid. Thus, the hypothesis is that the increased ratio of n6:n3 PUFAs in westernized diet may have contributed to the increased asthma incidence.

**The assessment of diet in epidemiologic studies**

Several methods are used to assess dietary exposures in epidemiologic studies (Table 1) [28]. The most commonly used methods include 24-hour recall interviews [29], diet records [29], food-frequency questionnaires [30,31], and measurements of nutrient biomarkers [32]. Trained interviewers administer 24-hour recall interviews and ask subjects to report everything they had to eat or drink in the past 24-hour period [29]. This method
depends on the short-term memory of the subject. The interview may be conducted over the telephone or in person, and it is important to have skilled interviewers to probe for additional foods and to do so in a neutral manner so as not to influence the subjects’ responses. With properly trained interviewers, high-quality dietary information can be collected. However, the use of such interviewers is expensive and impractical for large-scale epidemiologic studies. Interactive, computer-based 24-hour recall software programs are being developed to circumvent these limitations [33]. The food-record or food-diary method is similar to the 24-hour recall method, except that subjects record actual food and drink intake prospectively on 1 or more days [29]. Food records are quantified by asking the subject to either weigh the foods or determine volume using common household measuring tools. Assistance may be provided by the use of photographs. This prospective record minimizes reliance on memory and does not require trained interviewers. However, this method requires a reasonably high level of subject literacy and motivation, and requires some level of training in recording complete and accurate food intake. Furthermore, food records done on consecutive days may be correlated and may introduce bias in the measurement. Both the 24-hour recall and the food-record methods may not capture seasonal variation of diet or may not reflect usual long-term diets.

Table 1
Methods for assessment of diet and nutrition in epidemiologic studies

<table>
<thead>
<tr>
<th>Method</th>
<th>Pro(s) and con(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>24-hour recall</td>
<td>Pro: relatively precise (recent memory); relatively low participant burden</td>
</tr>
<tr>
<td></td>
<td>Con: may not reflect long-term diet; requires well-trained interviewers; nutrient analysis may be laborious</td>
</tr>
<tr>
<td>Diet record</td>
<td>Pro: precise record of intake over several days; recall error and bias are reduced because of prospective nature</td>
</tr>
<tr>
<td></td>
<td>Con: requires high level of subject literacy and motivation; may not capture long-term diet</td>
</tr>
<tr>
<td>Food-frequency questionnaire</td>
<td>Pro: applicable to large cohorts; assesses long-term diet; ease of administration allows for repeat measurements to capture changes in diet over time; provides information on large numbers of foods; relatively cheap to analyze and calculate nutrients</td>
</tr>
<tr>
<td></td>
<td>Con: population-specific; food list needs to be validated in a particular population to ensure that main foods are captured</td>
</tr>
<tr>
<td>Biomarker</td>
<td>Pro: precise measure of short-term status, depending on nutrient and nutrient half-life; may be the only reliable measurement of nutrient exposure</td>
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<tr>
<td></td>
<td>Con: invasive; requires collection of biological sample (blood, hair, nail)</td>
</tr>
</tbody>
</table>
These limitations may be reduced by performing these measurements on multiple days over several months of the year.

Food-frequency questionnaires are the most frequently used method for many epidemiologic studies [30,31]. They consist of a list of foods and beverages that represent the major contributors to the diet of the population being studied and a frequency response to report how often each food is consumed. Food-frequency questionnaires should be validated for a particular population or ethnicity because lists of foods and beverages may be specific to a particular group (eg, young children usually eat a more limited variety of foods compared with adults; recent immigrants tend to seek out foods native to their country of origin). Food-frequency questionnaires are easily administered in person or mailed to subjects. They provide information on usual intake of a large number of foods, food groups, and supplements; are substantially less expensive than other methods of dietary assessment; and can be administered repeatedly over several years to capture diet changes over time. From responses to the questionnaire, individual nutrient intake can be calculated based on the known nutrient content of foods. Alternatively, analyses based on usual intake of foods taken directly from the responses to the questionnaires (ie, frequency of intake of fruits and vegetables) can also be performed.

Biochemical markers of dietary intake are also commonly used in epidemiologic studies [32]. In many cases, these biomarkers are used to validate information obtained from food-frequency questionnaires. However, they are also used to indicate the status of the individual with regard to the nutrient of interest. In the case of some nutrients, biochemical indicators are the only reliable markers of nutrient status. For example, because selenium content of soil varies from area to area, the selenium content of similar foods obtained from different places can vary up to 100-fold. While these biomarkers can be considered as unbiased indicators of nutrient intake, many issues must be considered before using them for analyses of diet–disease associations. Biomarkers must accurately reflect nutrient intake, but this is not always the case, as genetic variation, lifestyle factors, and intake of other nutrients, among many other considerations [32], may affect the level of the nutrient of interest. Additionally, knowledge of the half-life of the biomarker is necessary for interpretation of findings (ie, short-term versus long-term exposure).

**Evidence for the association between diet and asthma**

Many studies have examined the association between various nutrients or foods and asthma and asthma-related phenotypes, such as lung function, airway responsiveness, and symptoms. Most of these studies have been cross-sectional in design with a few prospective studies, and have been conducted in adults or in older children. Tables 2 and 3 summarize selected studies that have investigated dietary factors in relation to lung function,
asthma, and asthma-related symptoms. Studies that had large numbers of subjects were included, with emphasis on more recent findings, when available. Comprehensive tabular summaries are available in other recent reviews [16,17].

**Antioxidants**

Oxidative stress plays a central role in asthma pathogenesis [24] and dietary antioxidants improve oxidant defenses [34] against free radicals. Antioxidants, namely vitamin C, vitamin E, carotenoids, and flavonoids, have been the most widely studied nutrients with regard to asthma and allergies, either as individual nutrients or in analyses assessing fruit and vegetable intake. Vitamin C is found in vegetables (red and green peppers, broccoli, tomatoes, potatoes, and spinach), fruits (oranges, tangerines, strawberries, cantaloupes), and fruit juices [35]. Vitamin E is also found in fruits (apples and mangos), vegetables, vegetable oils, meat, poultry, nuts, and eggs [36]. The most abundant carotenoids in the North American diet are beta-carotene, alpha-carotene, gamma-carotene, lycopene, beta-cryptoxanthin, and lutein-zeaxanthin. Food sources of carotenoids include carrots, sweet potatoes, spinach, kale, collard greens, and tomatoes [37]. Flavonoids, a large family of compounds synthesized by plants, have a wide range of biologic activities, including antioxidant activities, participation in cell signaling pathways, and activities related to decreasing inflammation [38]. Flavonoids are found in fruits, vegetables, teas, soybeans, and legumes. In general, observational studies have shown a protective effect of these antioxidants on atopy and either lung-function asthma diagnosis or wheeze (see Tables 2 and 3). However, results across studies have differed, with some studies showing effects with one antioxidant and others showing effects with another. Most of these studies were cross-sectional and the few longitudinal studies [39–41] have also shown some protective effects of dietary antioxidants on asthma or lung-function decline.

Several intervention studies with antioxidants have also been conducted. A randomized placebo-controlled trial of vitamin C and magnesium supplementation for 16 weeks in 300 asthmatics on inhaled corticosteroids did not show any benefit on lung function, methacholine airway responsiveness, peak flows, or symptom scores [42]. A second study from the same group showed that supplementation with vitamin C but not magnesium had modest steroid-sparing effects in 92 asthmatics [43]. In a randomized placebo-controlled trial of vitamin E supplementation for 6 weeks in 72 asthma patients, no evidence of clinical benefit was found [44]. Several small trials have shown protective effects of vitamin C [45, 46], beta-carotene [47], and lycopene [48] on either exercise-induced bronchoconstriction or exercise-induced lung-function decrements.

Antioxidants given together may work better than individual supplementation, and there is evidence to suggest that antioxidants protect against
<table>
<thead>
<tr>
<th>Investigators</th>
<th>Cohort or country</th>
<th>Population and study design</th>
<th>Dietary assessment method</th>
<th>Association</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Antioxidant vitamins, carotenoids, and minerals</strong></td>
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<tr>
<td>Schwartz &amp; Weiss [125]</td>
<td>NHANES I, United States</td>
<td>2526 adults; cross-sectional</td>
<td>Food-frequency questionnaires and 24-hour recall</td>
<td>Positive association between dietary vitamin C intake and FEV&lt;sub&gt;1&lt;/sub&gt;; no association between vitamin C–rich vegetables and lung function</td>
</tr>
<tr>
<td>Chuwers et al [126]</td>
<td>CARET, United States</td>
<td>816 adult men with asbestos exposure; cross-sectional</td>
<td>Food-frequency questionnaires; serum β-carotene and retinol</td>
<td>Positive association between serum β-carotene and both FEV&lt;sub&gt;1&lt;/sub&gt; and FVC; weak positive association between serum retinol and both FEV&lt;sub&gt;1&lt;/sub&gt; and FVC; no association between intakes of these nutrients from food-frequency questionnaires and lung function</td>
</tr>
<tr>
<td>Hu &amp; Cassano [127]</td>
<td>NHANES III, United States</td>
<td>18,162 adults; cross-sectional</td>
<td>24-hour recall; serum vitamins C and E, β-carotene and selenium</td>
<td>Positive associations between dietary and serum antioxidants and FEV&lt;sub&gt;1&lt;/sub&gt;</td>
</tr>
<tr>
<td>Hu et al [128]</td>
<td>69 counties in rural China</td>
<td>3085 adults; cross-sectional</td>
<td>3-day weighed records; plasma vitamin C from pooled samples</td>
<td>Positive associations between dietary vitamin C and both FEV&lt;sub&gt;1&lt;/sub&gt; and FVC; pooled plasma vitamin C levels were positively associated with county mean FEV&lt;sub&gt;1&lt;/sub&gt;</td>
</tr>
<tr>
<td>Britton et al [129]</td>
<td>Nottingham, United Kingdom</td>
<td>2633 adults; cross-sectional</td>
<td>Food-frequency questionnaires</td>
<td>Positive associations between vitamin C and vitamin E and both FEV&lt;sub&gt;1&lt;/sub&gt; and FVC; intakes of vitamin C and E were correlated and there was no effect of vitamin E independent of vitamin C</td>
</tr>
<tr>
<td>Study</td>
<td>Location</td>
<td>Sample Size</td>
<td>Study Design</td>
<td>Outcome Measures</td>
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<tr>
<td>Dow et al [130]</td>
<td>Southampton, United Kingdom</td>
<td>178 elderly men and women; cross-sectional</td>
<td>Food-frequency questionnaires</td>
<td>Positive associations between vitamin E and both FEV₁ and FVC; no association for vitamin C and lung function</td>
</tr>
<tr>
<td>Butland et al [131]</td>
<td>Wales, United Kingdom</td>
<td>2512 men; cross-sectional</td>
<td>Food-frequency questionnaires</td>
<td>In multivariable models, positive association between vitamin E and FEV₁; no associations between intakes of vitamin C, magnesium, and β-carotene with FEV₁; Positive association between intake of apples and FEV₁</td>
</tr>
<tr>
<td>Ness et al [132]</td>
<td>East Anglia, United Kingdom</td>
<td>835 men and 1025 women; cross-sectional</td>
<td>Plasma vitamin C</td>
<td>Positive associations between plasma vitamin C and both FEV₁ and FVC in men only</td>
</tr>
<tr>
<td>Grievink et al [133]</td>
<td>MORGEN Study, Netherlands</td>
<td>6555 adults; cross-sectional</td>
<td>Food-frequency questionnaires</td>
<td>Positive associations between dietary vitamin C and β-carotene and both FEV₁ and FVC; no associations for dietary vitamin E and lung function; vitamin E associated with productive cough; β-carotene associated with wheeze</td>
</tr>
<tr>
<td>Tabak et al [134]</td>
<td>Finland, Italy, and Netherlands</td>
<td>Middle-aged men from Finland (n = 1248), Italy (n = 1386), and Netherlands (n = 691); cross-sectional</td>
<td>Diet history</td>
<td>Positive associations between vitamin C and β-carotene and both FEV₁ and FVC; positive association between vitamin E and FEV₁ in Finnish men only</td>
</tr>
<tr>
<td>Carey et al [39]</td>
<td>Health and Lifestyle Survey, United Kingdom</td>
<td>2171 British adults; longitudinal (7-y follow-up)</td>
<td>Food-frequency questionnaires</td>
<td>Subjects who decreased fruit consumption had greatest FEV₁ decline over 7 years</td>
</tr>
<tr>
<td>Britton et al [79]</td>
<td>Nottingham, United Kingdom</td>
<td>2415 adults</td>
<td>Food-frequency questionnaires</td>
<td>Subjects with higher magnesium intake had decreased airway responsiveness</td>
</tr>
</tbody>
</table>

*(continued on next page)*
Table 2 (continued)

<table>
<thead>
<tr>
<th>Investigators</th>
<th>Cohort or country</th>
<th>Population and study design</th>
<th>Dietary assessment method</th>
<th>Association</th>
</tr>
</thead>
<tbody>
<tr>
<td>McKeever et al [41]</td>
<td>Nottingham, United Kingdom</td>
<td>2633 subjects; cross-sectional and longitudinal (follow-up on 1346 subjects after 9 y)</td>
<td>Food-frequency questionnaires</td>
<td>Positive cross-sectional associations between vitamin C and magnesium intakes and FEV$_1$; higher vitamin C intake was associated with slower FEV$_1$ decline; no associations between vitamin A or vitamin E and lung function</td>
</tr>
<tr>
<td>Cook et al [135]</td>
<td>England and Wales</td>
<td>2650 children; cross-sectional</td>
<td>Plasma vitamin C</td>
<td>No association of vitamin C levels with lung function</td>
</tr>
<tr>
<td>Vitamin D</td>
<td>NHANES III, United States</td>
<td>14,091 adults aged ≥ 20 y</td>
<td>Serum 25(OH)D</td>
<td>Positive associations for 25(OH)D levels and both FEV$_1$ and FVC</td>
</tr>
<tr>
<td>Minerals</td>
<td>Hampshire, United Kingdom</td>
<td>138 men; cross-sectional</td>
<td>24-hour urinary sodium excretion</td>
<td>Increased odds for having PD20 ≤ 8 μmol in subjects with greater sodium excretion</td>
</tr>
<tr>
<td>Burney et al [64]</td>
<td>Latium region, Italy</td>
<td>2593 subjects aged 9–16 y; cross-sectional</td>
<td>Dietary questionnaire; urinary sodium and potassium levels</td>
<td>Positive association with table-salt use and symptoms but not with airway responsiveness; higher urinary potassium but not urinary sodium was associated with airway responsiveness in boys</td>
</tr>
<tr>
<td>Pistelli et al [66]</td>
<td>Northern England</td>
<td>234 male shipyard workers exposed to welding fumes; 121 male rural and 111 male urban dwellers; cross-sectional</td>
<td>24-hour urinary sodium excretion</td>
<td>Increased odds for methacholine airways responsiveness with greater sodium excretion among male urban dwellers only</td>
</tr>
<tr>
<td>Study</td>
<td>Study Details</td>
<td>Study Population</td>
<td>Study Design</td>
<td>Dietary Assessment</td>
</tr>
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<tr>
<td>Sparrow et al [67]</td>
<td>Normative Aging Study, United States</td>
<td>273 middle-aged to older men; cross-sectional</td>
<td>24-hour urinary sodium and potassium excretion</td>
<td>Positive relationship between potassium excretion and methacholine airway responsiveness; no association of sodium excretion and airway responsiveness</td>
</tr>
<tr>
<td>Gilliland et al [80]</td>
<td>Children’s Health Study, United States</td>
<td>2566 children aged 11–19 y; cross-sectional</td>
<td>Food-frequency questionnaires</td>
<td>Children with lower magnesium and potassium intakes had lower lung function indices; no effect of sodium intake</td>
</tr>
<tr>
<td><strong>Fatty acids</strong></td>
<td></td>
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<tr>
<td>McKeever et al [88]</td>
<td>MORGEN-EPIC Study, Netherlands</td>
<td>13,820 adults; cross-sectional</td>
<td>Food-frequency questionnaires</td>
<td>No association between n-3 fatty acids and FEV$_1$; inverse association between some n-6 fatty acids and FEV$_1$</td>
</tr>
<tr>
<td>Schwartz &amp; Weiss [84]</td>
<td>NHANES I, United States</td>
<td>2526 adults; cross-sectional</td>
<td>24-hour diet recall</td>
<td>Small but significant effect of fish intake on FEV$_1$; effect was stronger in nonsmokers; did not distinguish effects of different types of fish</td>
</tr>
<tr>
<td>Sharp et al [85]</td>
<td>Honolulu Heart Program, Hawaii, United States</td>
<td>6346 men; cross-sectional</td>
<td>Food-frequency questionnaires</td>
<td>Interaction between fish intake and smoking; lower decrements of FEV$_1$ due to smoking among high fish intake</td>
</tr>
<tr>
<td>Butland et al [131]</td>
<td>Wales, United Kingdom</td>
<td>2512 men; cross-sectional</td>
<td>Food-frequency questionnaires</td>
<td>No effect of fish intake on lung function</td>
</tr>
</tbody>
</table>

**Abbreviations:** 25(OH)D, 25-hydroxyvitamin D; CARET, Carotene and Retinol Efficacy Trial; EPIC, European Prospective Investigation into Cancer and Nutrition Study; FEV$_1$, forced expiratory volume in 1 second; FVC, forced vital capacity; MORGEN, Monitoring Project on Risk Factors for Chronic Diseases; NHANES, National Health and Nutrition Examination Survey; PD20, dose required to cause a 20% fall in FEV$_1$.  

611 DIETARY FACTORS AND THE DEVELOPMENT OF ASTHMA
Table 3
Selected epidemiologic studies relating dietary factors with asthma, asthma-related symptoms, and atopy

<table>
<thead>
<tr>
<th>Investigators</th>
<th>Cohort or country</th>
<th>Population and study design</th>
<th>Dietary assessment method</th>
<th>Association</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Antioxidant vitamins, flavonoids, and minerals</strong></td>
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<tr>
<td>Schwartz &amp; Weiss [136]</td>
<td>NHANES II, United States</td>
<td>9074 adults; cross-sectional</td>
<td>24-hour diet recall</td>
<td>Serum vitamin C inversely associated with wheezing and diagnosed bronchitis</td>
</tr>
<tr>
<td>Fogarty et al [137]</td>
<td>Nottingham, United Kingdom</td>
<td>2633 subjects with allergy skin test results and 2498 subjects with total IgE; cross-sectional</td>
<td>Food-frequency questionnaires</td>
<td>Higher vitamin E intake was inversely associated with total IgE concentrations and was associated with decreased odds for atopy</td>
</tr>
<tr>
<td>McKeever et al</td>
<td>NHANES III, United States</td>
<td>5858 adults and 4428 children</td>
<td>Serum levels of several nutrients</td>
<td>In adults, α-carotene, β-cryptoxantine, and vitamin E were inversely associated with atopy, but lycopene was positively associated with atopy; vitamin A increased the risk of atopy in children</td>
</tr>
<tr>
<td>Troisi et al [40]</td>
<td>Nurses Health Study, United States</td>
<td>77,866 nurses; longitudinal</td>
<td>Food-frequency questionnaires</td>
<td>Positive association between vitamin C supplement users and the risk for asthma; dietary vitamin E inversely associated with asthma; β-carotene weakly protective for asthma</td>
</tr>
<tr>
<td>Shaheen et al [138]</td>
<td>Greenwich, South London, United Kingdom</td>
<td>607 cases, 864 controls (adults)</td>
<td>Food-frequency questionnaires</td>
<td>Consumption of apples was inversely associated with asthma; selenium intake inversely associated with asthma; no association between intakes of vitamins C and E and asthma</td>
</tr>
<tr>
<td>Garcia et al [139]</td>
<td>Greenwich, South London, United Kingdom</td>
<td>607 cases, 864 controls (adults)</td>
<td>Food-frequency questionnaires</td>
<td>No association between intake of three major classes of flavonoids and asthma</td>
</tr>
<tr>
<td>Study Authors</td>
<td>Location</td>
<td>Sample Size</td>
<td>Data Collection</td>
<td>Diet Factor</td>
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<tr>
<td>Okoko et al [140]</td>
<td>Greenwich, South London, United Kingdom</td>
<td>2560 children aged 5–10 y; cross-sectional</td>
<td>Food-frequency questionnaires</td>
<td>Consumption of apple juice and bananas was negatively associated with wheeze but not asthma; fresh apple consumption was not associated with asthma or symptoms</td>
</tr>
<tr>
<td>Chatzi et al [141]</td>
<td>Menorca, Spain</td>
<td>460 children aged 6.5 y; cross-sectional</td>
<td>Food-frequency questionnaires</td>
<td>Vegetable intake was inversely associated with current wheeze and atopic wheeze; fish intake was inversely associated with atopy</td>
</tr>
<tr>
<td>Chatzi et al [142]</td>
<td>Crete, Greece</td>
<td>690 children aged 7–18 y; cross-sectional</td>
<td>Food-frequency questionnaires</td>
<td>Intake of local fruits and tomatoes was inversely associated with wheeze and allergic rhinitis but not atopy; adherence to the Mediterranean diet was inversely associated with allergic rhinitis</td>
</tr>
<tr>
<td>Sodium Demissie et al [143]</td>
<td>Montreal, Canada</td>
<td>187 cases and 145 controls aged 5–13 y</td>
<td>Food-frequency questionnaires</td>
<td>No association of usual salt intake with asthma or exercise-induced bronchospasm; positive association with methacholine airway hyperresponsiveness</td>
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<td>Fatty acids</td>
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<tr>
<td>Laerum et al [86]</td>
<td>RHINE; Norway, Iceland, Denmark, Estonia, and Sweden</td>
<td>12,345 adults</td>
<td>Food-frequency questionnaires</td>
<td>Low current fish intake was associated with greater odds of asthma and wheeze; for intake of cod oil, there was a U-shaped association with asthma</td>
</tr>
<tr>
<td>Tabak et al [87]</td>
<td>ISAAC-2, Netherlands</td>
<td>598 children aged 8–13 y; cross-sectional</td>
<td>Food-frequency questionnaires</td>
<td>Fish intake was inversely associated with current asthma and with atopic asthma with bronchial hyperresponsiveness; intake of whole grains was inversely associated with atopic asthma with bronchial hyperresponsiveness</td>
</tr>
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**Abbreviations:** ISAAC, International Study of Asthma and Allergies in Childhood; NHANES, National Health and Nutrition Examination Survey; RHINE, Respiratory Health in Northern Europe.
exposure to outdoor air pollution, particularly ozone exposure. In a randomized, double-blind crossover study of 47 street workers in Mexico City, supplementation of vitamin C, vitamin E, and beta-carotene protected against ozone-induced decrements in lung function [49]. A study from the same group showed that supplementation with vitamin C and vitamin E attenuated the effects of ambient ozone exposure on lung function indices in Mexican children [50]. In a randomized, double-blind crossover study, 17 adult asthmatics were supplemented with both vitamin C and vitamin E, then exposed to ozone during moderate exercise, after which bronchial provocation testing with sulfur dioxide was performed [51]. Antioxidant supplementation protected against ozone-induced bronchial hyperresponsiveness.

Overall, observational studies have shown protective effects of antioxidants on asthma-related phenotypes, but large trials of antioxidant supplementation have not shown any benefit for asthma symptoms or control. McKeever and Britton [16] have discussed issues related to these discrepancies between observation studies and intervention trials. Some of these issues relate to accuracy of measurements of the dietary intakes in observational studies, confounding by other exposures linked with diet, and lack of effectiveness of single-nutrient supplements if other nutrients are important or if foods are more important than the individual nutrient. It is also possible, as the smaller intervention trials show, that antioxidant effects may be seen in only particular subsets of asthmatics (eg, exercise-induced asthmatics) or in response to specific exposures (eg, ozone exposures). Alternatively, because the intervention trials have been conducted in adults or children who have asthma, they do not address the issue of primary prevention of asthma. Early-life programming leading to predisposition to adult diseases is a growing area of research [52]. It is possible that the effects of diet—including all nutrients—on asthma may occur much earlier in life than researchers have assumed [18]. Studies of diet in early life and related effects on asthma incidence are reviewed later in this article.

**Vitamin D**

Vitamin D is both a nutrient and a hormone. However, unlike usual nutrients, vitamin D does not naturally occur in foods that humans eat, except in oily fish and fish liver oil, egg yolk, and offal [53]. Therefore, most of the vitamin D that we ingest comes from fortified foods (In the United States, milk; some milk products, such as yogurt and margarine; and breakfast cereals are fortified with vitamin D [54,55].) and from supplements. The Institute of Medicine [54] currently recommends intakes of 200 IU/d from birth through age 50 years, 400 IU/d for those aged 51 to 70 years, and 600 IU/d for those over 70 years. However, there is now widespread consensus that these recommendations are woefully
inadequate for overall health [56]. From an evolutionary standpoint, humans do not require vitamin D in the food supply because it is effectively produced in the skin on exposure to sunlight in the UV-B range. Because people in westernized countries now spend most of their time indoors, it has been postulated that vitamin D deficiency may explain a large portion of the asthma epidemic [57]. Vitamin D may reverse steroid-resistance in asthmatics through induction of IL-10–secreting T-regulatory cells [58], and vitamin D has been shown to regulate expression of many genes in bronchial smooth muscle cells, including genes previously implicated in asthma predisposition and pathogenesis [59]. Two recent analyses have related vitamin D with lung function. The first, published in abstract form, involved 2112 adolescents from 12 cities in the United States and Canada [60] and found that vitamin D intake was inversely associated with lung function. The second study was a cross-sectional analysis of 14,901 adults from the National Health and Nutrition Examination Survey [61]. Circulating serum vitamin D levels (25-hydroxyvitamin D3) were measured from stored samples and subjects with higher vitamin D levels had higher values of forced expiratory volume in 1 second (FEV₁) and forced vital capacity (FVC). There are no trials of vitamin D supplementation in subjects with asthma.

Minerals

Sodium

In 1987, Burney [62,63] highlighted an association between regional table-salt sales and asthma mortality, and subsequent studies have shown a positive relationship between salt intake and the presence of airway hyper-responsiveness [64,65]. However, this finding has not been universal [66,67]. Thus, it remains unclear whether salt is directly associated with asthma or is merely a marker for a diet that increases the risk for asthma. A recent study suggests that dietary salt loading enhances airway inflammation [68]. A Cochrane Database review of six randomized controlled trials did not find any significant effect of dietary salt restriction on asthma treatment or management [69]. No longitudinal studies have addressed the association between salt intake and development of asthma.

Selenium

Selenium is a trace mineral involved in antioxidant defenses as a coenzyme of glutathione peroxidase, which recycles glutathione. Plant foods are the major dietary sources of selenium in most countries [70]. Assessment of selenium intake is difficult because the selenium content of the same type of foods varies widely depending on where the food is obtained, owing to the variability in selenium content of soil [32]. Several case-control studies have documented lower selenium blood levels in asthmatic subjects compared with nonasthmatics [71–73]. In a small trial of 12 adult
asthmatics, selenium supplementation for 14 weeks showed improvement in clinical parameters but not in objective markers of asthma [74]. A recent larger trial of 197 adult asthmatics, most of whom were on inhaled steroids, did not show any clinical benefit of selenium supplementation over 24 weeks [75].

Magnesium

Magnesium is a cation with modulatory effects on smooth muscle cell contractility [76], such that hypomagnesemia induces contraction (bronchoconstriction) while hypermagnesemia induces relaxation (bronchodilation). This potential bronchodilatory property of magnesium has led to its use in emergency department care of acute asthma exacerbations [77]. Green vegetables, such as spinach, are good dietary sources of magnesium [78]. Cross-sectionally, evidence suggests that higher magnesium intakes are associated with decreased airway hyperresponsiveness and symptoms in adults [79] and decreased lung function in children [80]. Clinical trials of supplementation with magnesium (given with vitamin C) did not show any clinical benefit on lung function, symptoms, or on ability to decrease steroid dose in asthmatics [42,43].

Polyunsaturated fatty acids

While there is some evidence relating diets rich in saturated fats from milk and dairy products with a reduced risk for asthma in preschool children [81] and young adults [82], most studies have investigated intakes of n3 and n6 PUFAs. The anti-inflammatory role of n3 PUFAs and the proinflammatory role of n6 PUFAs are well documented [83]. Briefly, n6 PUFAs (arachidonic acid and linoleic acid) give rise to the eicosanoid family of mediators (prostaglandins, thromboxanes, leukotrienes, and related metabolites), which have proinflammatory actions and regulate the production of inflammatory cytokines, while n3 PUFAs (eicosapentaenoic acid and docosahexaenoic acid) decrease the production of arachidonic acid–derived eicosanoids and inflammatory cytokines (tumor necrosis factor, IL-6), and decrease the expression of adhesion molecules involved in inflammation.

Several large cross-sectional studies have found positive associations between fish intake and lung function [84,85], and inverse associations between fish intake and asthma [86,87]. However, Butland and colleagues did not find any effect of fish intake on lung function in 2512 men. McKeever and colleagues [88] found no association between n3 PUFA intake and lung function, although there were inverse associations between some n6 PUFAs and FEV1. Other recent studies have likewise not found associations between measured n3 PUFAs and asthma [89,90]. Several small trials of fish oil supplementation have shown mixed results [91–94]. Results of trials of fish oil supplementation in the prenatal and early-life period are presented below.
Prenatal diet and nutrition

There is growing recognition that prenatal and early-life exposures, including exposures related to diet and nutrition, may have a role in the development of many adult diseases [52]. Research into the developmental origins of health and disease has focused mainly on obesity, the metabolic syndrome, and cardiovascular disorders, but asthma and other respiratory disorders are also affected by early exposures [95,96]. Despite the difficulty in diagnosing asthma in very young children, the available epidemiologic evidence suggests that about half of all cases of childhood asthma are diagnosed by age 3 years and 80% of all asthma cases are diagnosed by age 6 [97,98]. Thus, it is clear that early-life factors play a role in the inception of the disease. However, identifying the causative early-life factors remains challenging. Smoking in pregnancy, through its effects on lung development in utero, is the only definite prenatal risk factor for asthma that has been identified to date [99]. In the past few years, several studies have been published that have investigated the effects of maternal diet in pregnancy on immune outcomes and wheezing illnesses in young children (Table 4). It has been hypothesized that specific nutrients may exert their effect at the critical time period when the fetal immune system and lung development is occurring [18,57,100].

Devereux and colleagues [101] studied the T helper cell proliferative responses of cord blood mononuclear cells from a sample of 223 neonates from Aberdeen, Scotland, and found that higher maternal intakes of vitamin E were associated with lower cord blood mononuclear proliferative responses to timothy grass and house dust mite, compared with mothers whose intakes were in the lowest tertile of vitamin E. Follow-up of these children in the larger cohort of over 1000 children has found that higher maternal vitamin E intakes were associated with decreased risks for wheezing and asthma in the children at 2 and 5 years of age [102,103]. Maternal vitamin E (both intake during pregnancy and plasma level of $\alpha$-tocopherol at delivery) was also inversely associated with levels of exhaled nitric oxide (a marker of airway inflammation) and positively associated with post-bronchodilator FEV$_1$ in a subset of the 5-year-old children. Additionally, maternal zinc intake was also associated with decreased risks for several asthma-related phenotypes at 5 years. While maternal vitamin C was associated with increased risks for wheezing phenotypes at 2 years, this association disappeared when the children turned 5 years old. In a cohort from Boston, Massachusetts, Litonjua and colleagues [104] similarly found that higher maternal antioxidant intakes (vitamin E and zinc) were also associated with decreased risks of any wheeze and persistent wheeze in 1290 2-year-old children.

A subsequent study from the Scottish cohort reported that mothers who consumed more apples and fish in pregnancy had children who were less likely to wheeze [105]. A study of 631 children from Ireland also showed...
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<td>Martindale et al [102]</td>
<td>SEATON, Aberdeen, Scotland</td>
<td>1374 2-y-old children</td>
<td>Food-frequency questionnaire</td>
<td>Maternal vitamin E intakes were negatively associated with wheeze in the absence of a cold; maternal vitamin C intakes were positively associated with ever wheeze</td>
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<td>Devereux et al [103]</td>
<td>SEATON, Aberdeen, Scotland</td>
<td>1253 5-y-old children; 478 5-y-old children with lung function measures</td>
<td>Food frequency questionnaire; maternal $\alpha$-tocopherol levels in pregnancy</td>
<td>Maternal intakes of vitamin E and zinc were negatively associated with wheeze and asthma in 5-y-old children; maternal plasma $\alpha$-tocopherol levels were positively associated with FEV$_1$ in the 5-y-old children</td>
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<td>Litonjua et al [104]</td>
<td>Project Viva, Boston, Massachusetts, United States</td>
<td>1290 children</td>
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<td>Maternal intakes of vitamin E and zinc were negatively associated with any wheeze and recurrent wheeze in 2-y-old children</td>
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<td>Shaheen et al [107]</td>
<td>ALSPAC, United Kingdom</td>
<td>2044 children for wheezing analyses; 2173 children for eczema analyses</td>
<td>Cord blood levels of trace elements and minerals</td>
<td>Cord blood selenium was negatively associated with persistent wheeze up to 42 months of age; cord blood iron was negatively associated with late-onset wheeze (wheeze occurring at 30–42 mo but not before 6 mo) and eczema at 18–30 mo</td>
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<td>Devereux et al [108]</td>
<td>SEATON, Aberdeen, Scotland, United Kingdom</td>
<td>1282 2-y-old children and 1167 5-y-old children</td>
<td>Maternal and cord blood plasma selenium and erythrocyte glutathione peroxidase</td>
<td>Maternal and cord blood plasma selenium were inversely associated with wheezing in 2-y-old children; however, maternal and cord blood selenium levels were not associated with asthma or wheeze at 5 y; no associations between erythrocyte glutathione peroxidase and wheezing were found</td>
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<td><strong>Vitamin D</strong></td>
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<td>Devereux et al [112]</td>
<td>SEATON, Aberdeen, Scotland, United Kingdom</td>
<td>1253 5-y-old children</td>
<td>Food-frequency questionnaire</td>
<td>Maternal intakes of vitamin D were negatively associated with ever wheeze, wheeze in the past year, and persistent wheeze in 5-y-old children</td>
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<td>Camargo et al [111]</td>
<td>Project Viva, Boston, Massachusetts, United States</td>
<td>1194 children</td>
<td>Food-frequency questionnaire</td>
<td>Maternal intakes of vitamin D were negatively associated with recurrent wheeze; no association with eczema</td>
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<td>Gale et al [114]</td>
<td>Southampton, United Kingdom</td>
<td>440 infants for eczema; 178 for asthma</td>
<td>Maternal 25(OH)D level</td>
<td>Maternal 25(OH)D levels were positively associated with eczema and asthma, although only univariate associations were presented</td>
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<td>Yu et al [118]</td>
<td>Linköping, Sweden</td>
<td>68 infants (33 babies born to allergic mothers and 35 babies born to nonallergic mothers) followed to 6 y</td>
<td>Cord blood levels of fatty acids</td>
<td>Significant correlations between various n-6 fatty acids and between n-3 and n-6 fatty acids were found in cord blood of children who did not develop allergic disease (allergic dermatitis or asthma) by 6 y of age; these correlations were not found in cord blood of children who developed allergic disease by 6 y of age</td>
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<tr>
<td>Galli et al [119]</td>
<td>Rome, Italy</td>
<td>57 infants</td>
<td>Cord blood and infant levels of fatty acids</td>
<td>Lower AA and dihomo-gamma-linolenic acid in cord blood among infants who developed atopy (10 eczema and 3 asthma) in the first year of life</td>
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<tr>
<td>Newson et al [120]</td>
<td>ALSPAC, United Kingdom</td>
<td>Wheezing analyses: 1191 and 2764 infants for cord and maternal analyses, eczema analyses: 1238 and 2945 infants for cord blood and maternal analyses, respectively</td>
<td>Maternal and cord blood red cell fatty acid measurements</td>
<td>Cord blood ratio of AA:EPA was positively associated with eczema (at 18–30 mo), ratio of LA:ALA was positively associated with late-onset wheeze (wheeze occurring at 30–42 mo but not before 6 mo), and ratio of ALA:n3 was negatively associated with late-onset wheeze; however, after adjustment for multiple testing, these associations were no longer significant; no associations between maternal red cell fatty acids and infant outcomes</td>
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<td>Dunstan et al [124]</td>
<td>Fish Oil Supplementation Trial, Perth, Australia</td>
<td>83 pregnant women (40 with fish oil supplementation and 43 with olive oil supplementation) and their 1-y-old children</td>
<td>Clinical trial of fish oil supplementation in 83 atopic pregnant women</td>
<td>Reductions in positive skin tests to allergens, although not statistically significant; nonsignificant reduction in risks for recurrent wheeze and asthma</td>
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<td><strong>Foods</strong> Willers et al [105]</td>
<td>SEATON, Aberdeen, Scotland, United Kingdom</td>
<td>1253 children</td>
<td>Food-frequency questionnaire</td>
<td>Maternal intakes of apples were negatively associated with wheeze and asthma; maternal intakes of fish were negatively associated with eczema</td>
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<td>Fitzsimon et al</td>
<td>Ireland</td>
<td>631 3-y-old children</td>
<td>Food-frequency questionnaires</td>
<td>Maternal intakes of fruits and vegetables were inversely associated with asthma; maternal fat intake increased the risk for asthma</td>
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**Abbreviations:** 25(OH)D, 25-hydroxyvitamin D; AA, arachidonic acid; ALA, α-linolenic acid; ALSPAC, Avon Longitudinal Study of Pregnancy and Childhood; EPA, eicosapentaenoic acid, SEATON, Study of Eczema and Asthma To Observe the Effects of Nutrition.
that higher fruit and vegetable intake in pregnancy decreased the risk for asthma by age 3 [106], although it is unclear whether the food-frequency questionnaire was administered to the mothers during pregnancy or at recruitment when the children were 3 years old. That study also found that higher added fats (from butter, margarine, and other spreads; salad dressings; and mayonnaise) in maternal diet in pregnancy increased the risk for asthma in the 3-year-old children. The United Kingdom Avon Longitudinal Study of Pregnancy and Childhood cohort study reported low umbilical cord selenium concentrations to be associated with an increased likelihood of persistent wheeze in 2044 children in the first 42 months of life [107]. The Scottish group also found an inverse relationship between maternal and cord blood plasma selenium and wheeze phenotypes in 2-year-old children, but this relationship disappeared when the children turned 5 years old [108]. There are no published intervention studies of prenatal antioxidant supplementation and asthma in children.

Vitamin D is both a nutrient and a hormone, and it is important for immune regulation [109]. Deficiency in vitamin D is widespread and has been postulated to contribute to the rise in asthma [110]. Two birth cohorts have assessed maternal vitamin D intake in pregnancy and wheezing symptoms in 3- to 5-year-old children. In the Boston cohort of 1194 3-year-old children, children born to mothers who had intakes of vitamin D in the highest quartile had significantly decreased risks of recurrent wheezing (odds ratio 0.39; 95% CI 0.25–0.62) compared with children born to mothers in the lowest quartile of vitamin D intake [111]. In the Aberdeen [112] cohort, similar findings were obtained in 1212 children. Children born to mothers with vitamin D intakes in the highest quintile had significantly decreased risks for persistent wheeze (odds ratio 0.33; 95% CI 0.11–0.98) compared with children born to mothers with vitamin D intakes in the lowest quintile. Two other studies have suggested that vitamin D intake increases the risk for asthma. In the Northern Finland Birth Cohort, data on vitamin D supplementation in the first year of life and subsequent asthma and atopy outcomes at 31 years of age were obtained on 7648 subjects [113]. The risk for atopy (odds ratio 1.33; 95% CI 1.07–1.64) and allergic rhinitis (odds ratio 1.33; 95% CI 1.12–1.58) at age 31 years was higher in subjects who had received regular vitamin D supplementation in the first year compared with other subjects. However, there was no assessment of maternal vitamin D intake and no assessment of vitamin D intake in the intervening period between the first year of life and age 31 years. A second study measured circulating vitamin D levels in pregnant women and reported that higher circulating vitamin D levels in pregnant women were associated with increased risks for eczema at 9 months and asthma at 9 years [114]. However, results were reported only in univariate models without adjustment for potential confounders, and there was significant loss to follow-up in the cohort, especially at 9 years. Thus, the question of whether vitamin D is a protective or a risk factor for asthma in children remains unresolved.
Future studies will need to account for factors that affect vitamin D levels, such as use of sunscreen, time spent outdoors in the sun, season of the year, and skin color. There are no published intervention studies of vitamin D supplementation in pregnancy.

A few studies have related childhood asthma and atopic disease to maternal dietary intake of foods rich in n3-fatty acids (eg, fish intake), but these studies were limited by retrospective recall of diet in pregnancy (eg, mothers were asked to recall diet 5–20 years previously) [115,116]. Several studies have measured cord blood levels of PUFAs and related these to immune responses in cord blood mononuclear cells. Gold and colleagues [117] investigated cord blood PUFA levels in 192 cord blood samples and found that increased cord plasma eicosapentaenoic acid (n-3) and arachidonic acid (n-6) were both associated with decreased proliferative and IFN-\(\gamma\) responses, in addition to increased IL-13 responses. Several observational studies of cord blood PUFAs and atopic disease development in childhood have been conducted with variable results [118–120]. More importantly, there have been two intervention studies using fatty acids to prevent asthma or allergies. The first was conducted in the Childhood Asthma Prevention Study [121–123]. In 616 children at risk for atopic disease, the dietary intervention was 500 mg daily of n-3 PUFA–rich fish oil, in addition to n-3–rich oils and spreads for the family, compared with the controls, who received placebo and n-6–rich oils and spreads for the family. This study found a reduction in wheeze symptoms at 18 months [122] but minimal, if any, beneficial effect on asthma or atopic disease at 3 years [121]. The associations were null at 5 years [123]. However, this study applied the intervention postpartum. Dunstan and colleagues [124] supplemented the diets of 40 pregnant atopic women with n-3 PUFA–rich fish oil from 20 weeks’ gestation, and 43 control women received olive oil. Fish oil supplementation was associated with a general reduction in cord blood mononuclear cell cytokine responses (IL-5, IL-10, IL-13, and IFN-\(\gamma\)). In addition, maternal supplementation with fish oil was associated with borderline significant reduction in atopic sensitization to egg in 1-year-old children. No further follow-up studies on these children have been published.

Summary

Changes in diet predating the increases in asthma and allergy that have occurred in westernized countries are postulated to be among the reasons for the asthma epidemic. Many observational studies in adults and children have implicated deficiencies in specific nutrients as potential causes of the asthma and allergy epidemic. However, these have not been borne out in large intervention trials of supplementation with specific nutrients in asthmatics. Smaller trials, specifically with antioxidant supplementation, suggest that the effects may be limited to subsets of asthmatics (eg, exercise-induced
asthmatics) or as modifiers of the effects of pollutants (e.g., ozone). Alternatively, because asthma and allergies have their beginnings in early life, it is likely that nutrients may exert their effects in utero and in very early life, when the immune system and the lungs are not yet fully developed. Several observational studies have shown effects of maternal diet in pregnancy, and two intervention trials on n3 PUFA supplementation have been conducted. More studies are needed to further clarify the effects of diet in early life on the inception of asthma and allergies.

References

Dietary Factors and the Development of Asthma


Living on a Farm: Impact on Asthma Induction and Clinical Course

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As with many other chronic conditions, asthma, atopic dermatitis, and hay fever are likely to be determined by multiple factors, some of which constitute intrinsic host characteristics such as gender, race, genetic predisposition, and atopy, and some of which consist of extrinsic, environmental influences. These various factors are likely to interact on many different levels. In addition, the developmental aspects of a maturing and growing organism from infancy through the toddler years to childhood, adolescence and adulthood have to be considered as the natural history of allergic conditions varies. Therefore, complex time-dependent interactions between genetic determinants and environmental exposures are likely to exist, which should be kept in mind when investigating potential determinants of asthma and allergies in diverse populations.

In general, reported rates of asthma, hay fever, and atopic dermatitis are higher in affluent, Western countries than in developing countries. The worldwide prevalence of allergic diseases was assessed in the 1990s by the large scale International Study of Asthma and Allergy in Childhood (ISAAC Phase I) \cite{1}. Between 20-fold and 60-fold differences were found between centers. In the more recent Phase II of ISAAC, which included objective measures of asthma and allergies, a wide variation in the prevalence of atopic sensitization across study centers was seen confirming the previous questionnaire-based observations \cite{2}. Interestingly, a strong correlation of the association between wheeze and atopic sensitization with the gross national income of the respective countries was found \cite{2}. Likewise, large geographic differences existed in the prevalence of respiratory symptoms,
asthma, bronchial responsiveness and atopic sensitization with high prevalence in English speaking countries and low prevalences in the Mediterranean region and Eastern Europe according to the European Community Respiratory Health Survey (ECRHS) studying adults aged 20–44 years [3]. The geographic pattern emerging from questionnaire findings was consistent with the distribution of atopy and airway hyperresponsiveness; the data support the conclusion that the geographic variation in asthma is real and not attributable to methodological factors such as the questionnaire phrasing, the skin testing technique, or the type of assay for the measurement of specific IgE. Thereby, the validity of ISAAC and ECRHS study instruments has clearly been demonstrated.

Within the global perspective, some comparisons seem particularly informative. Studies of populations with comparable ethnic backgrounds but with striking differences in environmental exposures may be especially revealing. In the past, the East German–West German comparisons showed that high levels of domestic and industrial air pollution were not related to increased asthma and allergy risk in East Germany [4]. More recently, studies in China among children living in Hong Kong and in mainland China, namely in Beijing and Urumqi, have yielded interesting results [5]. The children of Beijing reported significantly more asthma symptoms than those living in Urumqi, but children of Hong Kong had the highest prevalence of asthma and other allergic symptoms of all. Urumqi, Beijing, and Hong Kong represent communities at increasing stages of affluence and westernization, and the findings from these three cities can be interpreted as a reflection of a worldwide trend for increasing prevalence of asthma and allergies as westernization intensifies.

In many countries of the developing world, westernization goes along with urbanization and thus with a loss of rural living conditions. Recent studies performed in Mongolia, which is in transition from having rural, farming communities to being an industrial society, allow the investigation of such factors. The prevalence of allergic rhinoconjunctivitis and allergic sensitization was 9.3% and 13.6% in Mongolian villages, 12.9% and 25.3% in rural towns, and 18.4% and 31.0% in Ulaanbaatar city, respectively. Migration from villages to towns and to the large city of Ulaanbaatar influenced prevalence estimates. The risks of allergic rhinoconjunctivitis (adjusted odds ratio [aOR] = 0.43, 95% CI: 0.19–0.98) and allergic sensitization (aOR 0.26, 95% CI: 0.13–0.55) were lowest in subjects living in a village since birth and intermediate in subjects who had relocated from a village to a town (aOR for rhinoconjunctivitis 0.68, 95% CI: 0.36–1.27; aOR for sensitization 0.62, 95% CI: 0.35–1.12) compared with subjects living in a town since birth.

The farming environment

A somewhat similar approach has attracted attention in Europe and other affluent countries in recent years. Several studies have been performed
in rural areas in Europe, namely in Switzerland [6–8], Germany [7–9], Austria [7,8,10], France [11], Sweden [8,12,13], Denmark [14,15], Finland [16–18] and Britain [19]; the studies contrast the prevalence of asthma and allergic diseases in children and adults living on farms as compared with subjects also living in rural areas but not on farms. Almost all studies reported a decreased prevalence of hay fever and allergic rhinoconjunctivitis among farm children compared with non-farm children; studies that included objective measures of specific IgE antibodies (by skin prick tests or serum measurements) demonstrated the most significant results [20].

Findings relating to asthma and wheeze are somewhat less consistent. According to a large survey including over 10,000 schoolchildren in Germany [9], children of farmers had a lower prevalence of asthma (Odds ratio \( \text{OR} = 0.65, 95\% \text{ CI: 0.39–1.09} \)) and wheeze (OR = 0.55, 95% CI: 0.36–0.86), yet other surveys in Switzerland [6], France [11] and Finland [16] did not find significant differences between groups. Only three studies included measures of airway hyperresponsiveness and one of these studies used exposure to wood and coal heating as a proxy for farming [14,21,22]. In the Danish and German studies, the prevalence of airway hyperresponsiveness was significantly reduced among farm children compared with non-farm children [14,21]. A Canadian survey confirmed these findings [23]. To the authors’ knowledge, no study has shown an increased prevalence of airway hyperresponsiveness among children raised on farms.

Looking at adult farming populations, similar figures have been observed. In the European farmers’ study, the prevalence of allergic rhinitis was 14.0% (95% CI: 12.7–15.3%) in 20–44 year old animal farmers as compared with 20.7% (95% CI: 19.9–21.5%) among the participants of the European Community Respiratory Health Survey [24]. Likewise, the prevalence of asthma was significantly lower among animal farmers compared with the general population (1.3; 0.9–1.7 % versus 3.2; 2.9–3.5%, respectively). For asthma, these findings have been confirmed in Norway, the Netherlands, Denmark and Canada (British Columbia) [15,25–27]. Only the Norwegian study could not confirm a protective association between working on a farm and allergic rhinitis [25].

The studies referenced above were based on a cross-sectional design. Only two studies have used a prospective, longitudinal approach. In Canada, over 13,000 asthma-free children aged 0–11 years were surveyed and the incidence of physician-diagnosed asthma was determined prospectively two years later [28]. The two-year cumulative incidence of asthma was 2.3%, 5.3% and 5.7% among children living in farming, rural non-farming, and non-rural environments, respectively. From the multivariate analysis with adjustment for confounders, children from a farming environment had a reduced risk of asthma compared with children from rural non-farming environment with \( \text{OR} = 0.22 \) (95% CI: 0.07–0.74) and 0.39 (95% CI: 0.24–0.65) for children with and without parental history of asthma, respectively. In Austria, 1150 elementary school children (mean age of 7.8 years) were
recruited from nine different areas in 1994 and followed for three years [29]. Adjusting for potential confounders, parental farming was inversely related to the prevalence and new occurrence of skin prick test positivity (no farming 12.2%, part-time farming 6%, full-time farming 2.2% incidence; OR farming versus non-farming 0.34, 95% CI: 0.12–0.98). Furthermore, children living in a farming environment were more likely to lose their positive allergy skin prick test during follow-up (no farming 14.6%, part-time farming 50%, full-time farming 60% loss of sensitization; OR farming versus non-farming 8.06; 95% CI: 2.05–31.75). To date, no cohort study following subjects with and without farm contact from childhood to adulthood exists.

**Sources of protective exposures in farming environments**

Farming practices vary between farms and between countries; this diversity may contribute to the heterogeneity of farm effects on asthma across studies and countries (Fig. 1). Some investigators have attempted to identify individual exposures in farm surroundings contributing to the reduction in risk of asthma and allergic diseases. Initial observations from Germany and Switzerland showed that children from full-time farmers had lower risk of atopic disease than children of part-time farmers [6,9] suggesting a dose-response effect. Two recent studies conducted outside of Europe [30,31]
seem to suggest that an important component of the farm environment is livestock exposure because no protective effect of farming was observed among children living in a primarily crop farming region in Australia. This conclusion is supported by the findings of European studies where exposure to livestock was identified as an important contributor to the protective farm effect \[7,9,16,19\]. Interestingly, in the Austrian study, children who did not live on a farm but who had regular contact with farm animals also had a lower prevalence of allergic sensitization (13.5 % versus 34.8%) [10].

Another source of protection has been identified in a number of studies: the consumption of unpasteurized milk [7,19,31]. As with livestock exposure, this effect was not restricted to children living on a farm, but was also seen among non-farm populations consuming unpasteurized milk [19]. A recent, more in-depth analysis of the multicenter PARSIFAL study of rural areas in Europe has also shown significant inverse relations of a diagnosis of asthma with keeping pigs in addition to dairy farming (aOR = 0.57; 95% CI: 0.38–0.86) and the use of silage as fodder for the animals (aOR = 0.55; 95% CI: 0.31–0.98) [32].

European studies among adult farmers also gave some evidence that the protective effect of farming on atopic diseases might be more pronounced among animal farmers, with the strongest effect among pig and cattle farmers [26,33,34]. However, recent studies outside of Europe were less consistent [27,35,36]. While Douwes and colleagues [35] in New Zealand found all farmers – independent of whether they had livestock contact or not – to be protected from asthma; only those working with dairy had a significantly reduced risk for allergic rhinitis as compared with those without farm contact (Fig. 2). In Canada, living on a farm had an overall protective effect on asthma and allergic rhinitis. Taking intensity of livestock contact into account did not make a difference with respect to prevalence of asthma or allergic rhinitis [27]. Likewise, US farm women who worked with animals had the same prevalence of atopic and non-atopic asthma as those not working with animals [36]. Therefore, differences in farming practices as well as the size of farming operations have to be taken into account when studying the effect of different types of farming exposure on allergies and asthma.

**Timing of farming exposures**

There is increasing evidence to suggest that the effect of a given exposure strongly depends on the timing of this exposure. At least throughout infancy, childhood, and adolescence, the human organism is in a constant process of development and maturation. It is conceivable that these predefined processes display windows of accessibility and vulnerability toward extrinsic influences at certain stages of development. Moreover, prenatal factors may play a significant role either through mechanisms acting in utero or as epigenetic modulation of subsequent developmental trajectories. In the
Fig. 2. Current or childhood exposure to farming environments and (A) asthma prevalence, (B) prevalence of allergic rhinitis, and (C) prevalence of allergic sensitization (prick or specific IgE) during adulthood [15,25–27,35,38,40,41]. Adjusted ORs with 95% CIs as provided in the articles. Definition of symptoms may differ across studies.
PARSIFAL Study, the risk of atopic sensitization was not only influenced by a child’s exposure to the farming environment, but it was also strongly determined by maternal exposure to stables during pregnancy (aOR = 0.58; 95% CI: 0.39–0.86) [37].

Studies on allergic rhinitis among adults

A number of studies have addressed the association between childhood contact to farming environments and the prevalence of asthma and allergies during adulthood (see Fig. 2) [15,26,38–41]. All of the studies found an inverse association between being raised on a farm and the prevalence of allergic sensitization to common allergens, as well as allergic rhinitis, during adulthood. To further analyze the relevance of timing of exposure, several studies have assessed the potential interaction between childhood and adulthood exposure to farming environments and the prevalence of allergies and asthma during adulthood (Fig. 3) [15,26,27,35,36,38,39]. Across these studies, the protective effect of farming environments on respiratory allergies was largest when farm contact started during childhood and was sustained until adulthood. Several of these studies indicated modification of effects by farm contact during childhood. That is to say, the protective effect of farm contact during childhood and adulthood on respiratory allergy might be more than additive.

In these studies, childhood exposure was defined in various ways from living on a farm during the first year of life to living on a farm any time
Fig. 3. Combined effect of current and childhood exposure to farming environments and (A) asthma prevalence (B) prevalence of allergic sensitization/rhinitis during adulthood [26,27,35,36,39,41]. Adjusted ORs with 95% CIs as provided in the articles. Definition of symptoms may differ across studies. No/No, neither farm contact during childhood nor recent farm contact; No/Yes, no farm contact during childhood, recent farm contact; Yes/No, farm contact during childhood, no recent farm contact; Yes/Yes, farm contact during childhood and recent farm contact.
before the age of 18 years. One study tried to disentangle the relevance of different time periods of farming exposure during childhood and the effect on self-reported allergic rhinitis in adult life [42]. Overall, it was shown that the protective effect of regular visits to animal dwellings on respiratory allergy was largest when these visits started during the first 6 years of life. However, because the authors had to rely on self-reported onset of exposure, misclassification of exposure might have affected the results. For those people who started farm contact later than when they were 6 yrs old, only a weak protective effect on allergic rhinitis or sensitization was seen. Therefore, infant exposure seems to be of uppermost importance in the life course of allergic sensitization [43,44].

Assuming that farm contact during childhood is also a proxy for prenatal and infant exposure provides additional evidence for the importance of prenatal factors on the development of asthma and allergies. One recent study among 137 university employees, of whom 36% were working with laboratory animals, indicated that those with farm contact during infancy were protected from sensitization to occupational allergens later in life [45]. Likewise, among rural adults living in an agricultural area of Germany, occupational exposure to high molecular weight agents could not be shown to increase the risk of allergic sensitization. In contrast, such exposure was shown to be inversely related to allergic sensitization to common allergens [46].

One might wonder why those who stopped their contact to farming environments do not encounter the same protection as those with continuous farm contact. It might be an indication of a healthy worker bias, meaning that those with symptoms leave the farming environment [39,47,48]. Although this might partly explain the effect, the strengths of the relationship and the consistency of the association across studies cannot be explained by a self-selection into farming alone [35]. Another issue that has been discussed is that farmers tend to underreport symptoms [39]. However, as the findings are not only evident for self-reported symptoms but also for objective markers of disease (ie, allergic sensitization assessed by skin prick test or specific IgE), the underreporting of symptoms is an implausible explanation (see Fig. 3). It is more likely that the underlying cause of the observed interaction is a complex interplay between prenatal factors, early childhood exposures, and events encountered over the life course.

It was argued that the high prevalence of asthma and atopy among US inner-city populations with lower standards of hygiene contradicts the "hygiene hypothesis" [49,50]. Because several studies have indicated that obesity is not only associated with asthma but also with allergic rhinitis (for review, see Ref. [51]), the high prevalence of obesity in inner-city populations might help to understand these paradoxical observations. To test this hypothesis, data from 1861 adults living in a rural area of Lower Saxony (Germany) have been analyzed. Results indicated that obesity might diminish or even cancel out the protective effect of childhood farm contact later in life [52].
Further analyses suggested that the underlying association between adipokines and sensitization might be more pronounced in subjects with childhood farm contact [53].

**Studies on asthma among adults**

With respect to the association between farm contact and asthma, the findings across studies have been less clear-cut (see Fig. 3A). Interpreting the inconsistencies, one has to bear in mind that less than half of adult asthma is characterized by an eosinophilic response [54,55]. In many cases, asthma is associated with a neutrophilic inflammation, a condition for which the term “asthma-like syndrome” has been coined. Although there is good evidence that farming also protects from atopic asthma, farming exposures, especially long-term exposure to endotoxin, constitute a risk factor for non-atopic asthma [35,38,42,56–59].

**Microbial exposures**

If livestock and other farming exposures are associated with a decreased prevalence of asthma and atopy, then underlying exposures should be investigated next. Children exposed to livestock may be exposed to more allergens, bacteria, viruses and fungi than children without exposure to livestock. Yet, only few out of the many microbial exposures have been measured in farming environments so far. Bacterial substances, such as endotoxin from gram negative species and muramic acid, a component of peptidoglycan from the cell wall of all types of bacteria, have been found to be more abundant in mattress dust from farm children than non-farm children [60]. Likewise, extracellular polysaccharide (EPS) from *Penicillium* and *Aspergillus spp.* is more prevalent in farming households than non-farm households [60].

In the ALEX study, a multicenter study conducted in rural areas of Austria, Switzerland and Germany, endotoxin levels in dust samples from the children’s mattresses were inversely related to the occurrence of hay fever, atopic asthma, and atopic sensitization [61]. However, non-atopic wheeze was not significantly associated with endotoxin levels. In turn, independently of endotoxin concentrations, increasing mattress dust muramic acid levels were associated with a lower frequency of wheezing and asthma among rural school children in the ALEX study [62].

The inverse association found in the ALEX study between endotoxin and atopic wheeze was confirmed in the larger multicenter PARSIFAL survey performed in Sweden, the Netherlands, Germany, Austria, and Switzerland [63]. When restricting the PARSIFAL analyses to similar groups of children as in the ALEX study, farm and farm-reference children in Germany, Austria, and Switzerland, a decreased risk (aOR = 0.56, 95 %CI: 0.35–0.90) was
observed. After adjustment for glucans and EPS, the effect of endotoxin was, however, no longer significant. Since exposures to endotoxin, EPS, and glucans were moderately, but significantly, correlated, a firm conclusion about the degree to which specific agents contributed to the observed effect is precluded. Moreover, these microbial agents might be markers of a much broader spectrum of microbial agents. Muramic acid was not measured in the PARSIFAL study. In this study, all measured microbial compounds (ie, endotoxin, glucans, and EPS) did not explain the protective ‘farming effect’ which suggests that other, yet unknown, microbial exposures confer the protection seen in the farming environments. The results do, however, also suggest that mold components might modulate immune responses and thereby protect against allergic diseases, as was previously suggested for endotoxin [60].

This conclusion is in line with a study on the effects of endotoxin and fungal spores on atopy and asthma in adult farmers, in which fungal spores, rather than endotoxin, were inversely related to atopic wheeze [58]. Another study, among Dutch adult farmers, designed a job exposure matrix (JEM) to assign individual occupational exposure to endotoxins [64]. Using this JEM, endotoxin exposure was inversely related to self-reported symptoms of allergic rhinitis among the farmers. However, the prevalence of asthma symptoms increased with exposure. As no data on atopy were available, the authors could not stratify for atopic and non-atopic asthma. Furthermore, no data on fungal exposure were available. This study basically confirms an earlier case-control study among Dutch pig farmers [59]. While higher endotoxin levels were associated with a reduced odds ratio for sensitization to common allergens (0.03; 95% CI: 0.0–0.34), farmers with higher levels of endotoxin exposure were more likely to show airway hyperresponsiveness and to have reduced lung function. These studies give further evidence that farming exposure might not only be beneficial for the respiratory system. While protecting from respiratory allergies and atopic asthma, such exposure seems to pose a risk for non-atopic asthma in adulthood [24,38,57–59,64].

In the context of the hygiene hypothesis, some studies have indicated that foodborne and orofecal infections such as Helicobacter pylori, Toxoplasma gondii, and hepatitis A virus might as well protect from respiratory allergy [65–67]. Therefore, one explanation for the protective effect of the farming environment might be that exposure to microbial agents in the farm environment is a proxy for such infections. A study analyzing the association between farm animal contact, serologic markers of foodborne and orofecally transmitted infections, and atopy provided evidence that these mechanisms act independently [68]. It was shown that early contact with animal dwellings increases the likelihood of Toxoplasma gondii seropositivity. However, early contact to farm animals was still the strongest predictor of atopy (OR 0.49, 95% CI: 0.26–0.96).
Mechanisms of protection in farming environments

Few studies have investigated the immune responses in children raised on farms and compared those responses to immune responses in children raised in rural but non-farming environments. Since farming is associated with elevated exposure to microbes and/or microbial components, the Swiss arm of the ALEX study investigated whether growing up on a farm affects the expression of receptors for microbial compounds. Pathogen-associated molecular patterns (PAMPs), which are evolutionarily highly conserved structural components of microbes, are recognized by similarly conserved receptors of host innate immune systems, the pattern recognition receptors (PRRs). Examples of PAMPs are the bacterial compounds cited above, lipopolysaccharide (LPS, endotoxin), and muramic acid, a component of peptidoglycan, which is part of the cell wall of most bacteria. Examples of human PRRs are the human Toll-like receptors (TLRs) and CD14. To date, ten functional TLRs have been described in humans. By engaging TLRs, which belong to a first-line defense of innate immunity [69], signals required for initiating and modulating the adaptive immune response are also being generated [70]. In the context of the development of asthma and allergies, TLR4 (as receptor for LPS) and TLR2, which recognizes peptidoglycan of gram-positive bacteria, have received the most attention. Peripheral blood leukocytes from children of the ALEX population living on a farm were found to display increased expression of the genes for CD14, TLR2, and TLR4 [71] as compared with non-farm children.

The impact of farming on the expression of innate immunity genes was then further examined by the Swiss research team in 125 children of farmers and 127 children of non-farmers from the PARSIFAL study [37]. RNA was extracted from EDTA-treated blood, and expression of all TLRs and CD14 was determined by quantitative PCR (TaqMan). The results confirmed the initial observation suggesting that environmental exposures, in particular exposure to microbial components, affect the expression of genes encoding microbial ligand receptors [71]. A number of individual farm characteristics were related to the up-regulation of distinct TLR genes [32].

The Swiss research team then assessed whether changes in gene expression correlated with prenatal or postnatal exposure to farm factors. After adjusting for age, sex, family history of atopy, parental education, environmental tobacco smoke, maternal smoking during pregnancy, number of older siblings, contact with pets ever, study center, and current farm exposures, maternal exposure to stables during pregnancy (ie, prenatal exposure of the child) significantly correlated with an increase in the expression of TLR2 (geometric means ratio and 95% CI: 1.44 [1.04–1.98]), TLR4 (1.40 [1.07–1.83]) and CD14 (1.66 [1.18–2.33]) [37]. Interestingly, a dose response relation was seen. Expression of TLR2, TLR4 and CD14 increased with the number of different farm animal species the mother had contact with during
her pregnancy. Overall, these findings support the idea that prenatal environmental exposures affect the allergy and asthma risk of a child.

These findings also suggest a role for innate immunity in response to these environmental exposures.

With respect to sensitization to common aeroallergens, the underlying mechanisms may be even more complex. In the ALEX study, allergen-dependent switching patterns were reconstructed in vivo to identify the levels at which farm exposure acts to protect against atopy by assessing serum IgG1 to IgG4 and IgE levels to grass, cat, and mite allergens [72]. Farm exposure had complex allergen-specific effects on IgG1, IgG4, and IgE levels. Exposure protected against grass-specific responses at every step along the IgG1/IgG4/IgE switching pathway. Protection from cat responses was concentrated at the IgG1 level. For all allergens, failure to express IgG1 was associated with low prevalence of IgG4 or IgE responses. These findings suggest that the protective effects of farm exposure on atopic sensitization are allergen and switch stage specific. No counterbalancing, protective effect of IgG4 production as proposed in the context of urban cat exposure [73] has been seen in these farming environments.

The genetic background of children raised on farms and elsewhere in rural areas interacts with the environmental exposures. Polymorphisms in the genes for TLR4, TLR2 and NOD2 have furthermore been shown to interact with the farm environment, modulating the asthma and allergy protective effect [74]. Recently, a significant interaction between genetic variation in CD14/-1721 and farm milk consumption was found. Adjusted odds ratios for the association between farm milk and asthma varied between the genotypes: AA, 0.18 (95% CI, 0.07–0.47); AG, 0.47 (95% CI, 0.26–0.86); and GG, 0.98 (95% CI, 0.46–2.08). Similar patterns were observed for symptoms of allergic rhinoconjunctivitis and pollen sensitization. CD14/-1721 also modified the association between farm milk and CD14 gene expression. Taken together, these findings suggest that the protective effect of various farm exposures is modified by an individual’s genetic makeup. This is supported by two recent studies among adults. In these studies, the potential gene-environment interaction between the genes for CD14 has been assessed [11,75]. Both studies point toward an interaction between different positions in the promoter region of CD14 (-159T, -651T and -260T) and the prevalence of atopy in adult farmers [75] and the general population with childhood farm contact [11].

In conclusion, there is convincing evidence that a childhood spent on farms confers protection from respiratory allergies with a sustained effect into adulthood, particularly with continued exposure. The nature of individual protective exposures in the environments has not been elucidated. Studies so far suggest that, at least in childhood, contact with farm animals, their fodder, and their products (such as milk consumed directly from the farm) contribute to the “farm effect”. The underlying mechanisms are still ill defined, but they are likely to involve a number of steps in innate and adaptive
immunity. An individual’s genetic background modifies the effects of the environmental exposures.

References


Does the Social Environment Contribute to Asthma?

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The impact of the social environment on asthma has recently begun to receive increasing attention. This article reviews the current literature to investigate the impact of the social environment at three levels—the neighborhood level, the peer level, and the family level—and to explore pathways through which the social environment “gets under the skin” to impact asthma onset and morbidity. Research to date suggests that adverse social conditions at the neighborhood and family levels impact asthma morbidity through direct effects on physiologic systems as well as by altering health behaviors. The impact on asthma of social networks, such as friendships, is less clear and will need to be investigated further. Future research will need to take into account the impact of the social environment to develop more comprehensive models of asthma pathogenesis.

Does the social environment contribute to asthma?

Asthma is widely recognized as a complex disease with multiple contributing factors. These include environmental exposures, viral infections, and genetics, the roles of which have been well established [1–4]. However, in contrast to the above factors, the role of social factors in asthma has been less well-established. Clinical anecdotes have long existed describing patients whose asthma appeared to be exacerbated by social circumstances, such as a significant stressful life event. However, empirical evidence supporting this claim has only appeared more recently. This article provides an overview of studies that have addressed the role of the social environment in asthma,

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This work was supported by the Canadian Institutes of Health Research and the Michael Smith Foundation for Health Research.

0889-8561/08/$ - see front matter © 2008 Elsevier Inc. All rights reserved.
doi:10.1016/j.iac.2008.03.007 immunology.theclinics.com
and discusses the biological mechanisms by which social factors might influence the course of asthma.

What is the social environment?

The social environment includes the connections a person has to a larger social community. This could include interpersonal or close relationships with others, the daily social contacts an individual has with others, as well as an individual’s social position within a larger community. We argue that in considering the role of the social environment in asthma, it is important to acknowledge social factors at multiple levels. For example, the most proximal level of social environment is a person’s family. For many, family members are those with whom interactions take place daily and those with whom individuals have had their longest relationships. Friendships or peer relationships represent the next level of social connection. These are often close others who provide an important source of social support and companionship. At the broadest level are neighborhood connections. Neighbors provide a source of social contact, but may not be as close as family and friends. In addition, neighborhoods often provide a sense of social identity and community for many individuals. In this article, we discuss the role of the social environment at each of these levels—neighborhood, peer, and family levels—in affecting asthma.

Neighborhood effects on asthma

We highlight two social factors at the neighborhood level that have been linked to asthma: socioeconomic status (SES) and exposure to violence.

Socioeconomic status

Although SES likely reflects a number of nonsocial factors [5,6], including material resources, access to health care, and housing quality, it also contains a social component in that it indicates a person’s relative standing within a larger social community. This in turn affects how people perceive themselves within their social group [7], as well as how others interact toward them [8].

Across numerous studies, evidence shows that lower SES increases risk for morbidity among patients with asthma. For example, poor children and children from lower income families are significantly more likely to be hospitalized for asthma, to have greater asthma symptoms, and to have more severe asthma episodes compared with nonpoor and higher income children with asthma [9–11]. Fewer years of parent education also have been associated with greater risk of asthma hospitalizations and emergency department visits in children with asthma [12,13]. Longitudinal studies show similar patterns. For example, children whose fathers had less
prestigious occupations were more likely to be hospitalized because of asthma during the following 6 years compared with those whose fathers had more prestigious occupations [14]. In addition, neighborhoods with lower income levels and higher unemployment rates have been found to have higher rates of asthma hospitalizations [15–17]. Finally, population-based studies (which are distinct from the above studies that focus on children with pre-existing asthma) have also found that lower SES (as indicated by either parental education or neighborhood characteristics) is associated with greater risk of asthma-related emergency room visits, asthma hospitalizations, and more severe asthma in children [18,19].

In contrast, relationships between low SES and asthma onset are less clear. Some studies have shown that low SES is associated with an increased prevalence of asthma. For example, children whose parents have fewer years of education are more likely to have a physician diagnosis of asthma [19]. Children from poorer families are also more likely to have a diagnosis of asthma [9,11]. Children who live in inner-city or low-income neighborhoods are more likely to have current asthma [16,18,20,21]. However, other studies have found no evidence for an association between neighborhood SES and childhood asthma prevalence rates [22,23]. Meanwhile, some studies have found individuals in higher SES groups to be more likely to have an asthma diagnosis [24,25]. In sum, evidence that living in a low-SES environment increases the risk for morbidity among those already diagnosed with asthma is fairly strong, but evidence that low-SES environments contribute to asthma onset is less clear-cut.

Neighborhood characteristics

Intriguing evidence has emerged recently to suggest that certain negative social characteristics of neighborhoods may be detrimental to asthma. For example, exposure to violence represents a community-level stressor that can take a toll on health [26]. Previous research has documented that greater exposure to violence is associated with a greater number of symptom days in children with asthma, as well as a greater number of nights of lost sleep for caretakers because of their child’s asthma [27]. Similarly, greater problems in one’s neighborhood, such as problems with crime and gangs, have been associated with greater asthma symptoms in children [28]. In addition, exposure to violence moderated the relationship between physical environment exposures and asthma. Children were at greater risk for being diagnosed with asthma if they had high levels of exposure to both traffic-related air pollution and violence [29].

Explaining neighborhood effects

Why would the neighborhoods that people live in affect asthma? One possibility is that life in a low-SES or high-violence neighborhood is more stressful on a day-to-day basis. Life in a low-SES household may involve
multiple competing demands that are often unpredictable. For example, low-SES families may experience multiple pulls on their limited resources, such as trying to pay bills so that services to their home do not get shut off while trying to put enough food on the table and while trying to deal with problems in the house, such as a plumbing leak. Demands may also spill over from one domain into another, creating conflicts between domains for families. For example, parents may need to work additional shifts to make extra money for the family, but this takes away from time with children and creates pressures to find additional childcare options. Demands in low-SES households may also create unpredictability in families’ day-to-day lives. For example, low-SES children may not be able to count on a consistent schedule if parents must depend on unreliable public transportation for getting between work and home. Similarly, families that live in high-violence neighborhoods may also experience greater stress in their day-to-day lives. This may be because they have to constantly be vigilant for threats to their safety. This vigilance may be activated every time they leave their home, and may even extend to feeling unsafe in their home environment. As a result, families may have to change their pattern of activities. For example, if they do not feel safe, they might not leave the house to shop or for social activities. Hence life in low-SES or unsafe neighborhoods may be more stressful on a day-to-day basis [30]. In addition, families who live in low-SES or unsafe neighborhoods may have fewer material and social resources for coping with stressors when they arise, adding to the overall burden of stress for these individuals. In the section below on biological mechanisms, we discuss the notion that the experience of stress may directly influence biological systems in a way that has implications for asthma.

A second possibility is that neighborhood factors have effects on asthma by changing behaviors. For example, low-SES neighborhoods may have different social norms about the acceptability of certain health behaviors, such as smoking. If smoking is more prevalent and accepted in low-SES neighborhoods, individuals with asthma are more likely to both be exposed to secondhand smoke, as well as to be smokers themselves. Hence low-SES neighborhoods might increase the risk for health behaviors that are detrimental to asthma. In addition, neighborhoods with high levels of violence may create barriers to asthma management behaviors. For example, unsafe neighborhoods may make it difficult to fill asthma prescription medications in a timely fashion [31]. Finally, living in a neighborhood with frequent violence could affect asthma if individuals with asthma are more likely to spend time inside their homes, resulting in greater exposure to indoor allergens as well as more sedentary behaviors [31].

Social networks and asthma

A number of studies have asked whether the types of social networks or social support an individual has can impact asthma morbidity. Social
support can come from a number of sources, including friends, colleagues, teachers, physicians, and other asthma patients. Moreover, social support can be conceptualized both in terms of the perceived quality, or closeness, of social relationships, as well as the quantity—that is, the diversity or extensiveness—of one’s social networks. Patients with asthma report that social networks are quite valuable and helpful when it comes to managing their asthma [32,33].

Although patients perceive their social networks to be beneficial, the studies that have examined whether they are related to asthma outcomes have mixed conclusions. On the positive end, a number of studies have found social support to be associated with asthma outcomes. For example, poor confidant support and negative support were related to a greater likelihood of hospital admissions in adult patients with asthma [34]. Conversely, having better social contacts predicted fewer asthma symptoms and, to a lesser degree, better peak expiratory flow rate over the course of 3 weeks [35]. Social support may also be most effective as a buffer against stress. For example, individuals who experienced both more negative life events and low social support reported the most episodes of cold-induced asthma exacerbations [36]. Finally, Levy and colleagues [37] reported that after an unrelated intervention in youth with asthma in one of three housing developments studied, those whose social networks improved were more likely to experience a decrease in asthma symptoms relative to baseline measures.

Similarly, among children with asthma, the social networks of parents are related to clinical outcomes in their children. For example, parents who reported low social support were more likely to have children who were admitted to the emergency department [38] and who were at greater risk for continued atopic illness [39]. Conversely, families reporting good social support had children at reduced risk of both wheezing and asthma [40] and more likely to recover from atopic illness between the ages of 18 months and 3 years [39]. Weil and colleagues [41] also reported some evidence of an association between good social support in parents and marginally fewer days of wheeze in their children. That social support to the family can work in very practical ways was demonstrated in a Norwegian study that found that access to a specialized asthma health care facility was in part influenced by whether families of children with asthma had a physician in their social network [42].

Finally, in addition to morbidity outcomes, social support also may affect behaviors relevant to asthma. Two studies of youth with asthma found that receiving social support was related to better asthma self-management behaviors, such as greater medication adherence and more willingness to seek immediate help from other people in response to breathing problems [32,33]. Adults with asthma also reported their social network to be the main factor facilitating exercise and an active and healthy lifestyle [43].
In contrast to the above studies, a handful of studies have found no relationship between social support and asthma. Ngamvitroj and Kang [44] reported that social support was not a significant predictor of greater peak expiratory flow rate self-monitoring over the subsequent 3 months even though participants’ satisfaction with their social support was very good. A study of youth with asthma found that, whereas family support was associated with better pulmonary functioning and fewer asthma symptoms, peer support was not related to either of those factors [28]. Finally, one study investigating the risk factors for asthma mortality matched adults who died of asthma with a comparison group of patients with asthma who were hospitalized but did not die. None of the factors relating to people’s social networks, including bereavement, separation, or isolation, was found to be a significant risk factor for asthma mortality [45].

Finally, it is important to also consider the possibility that social networks may, in some circumstances, exert negative influences. For example, in certain situations, social networks may create peer pressure to engage in detrimental health behaviors. Precht and colleagues [46] found that high school students with asthma, in particular boys, were more likely than healthy students to smoke because of peer pressure, although the overall occurrence was rare. Chen and colleagues [28] also found that stronger peer support in youth with asthma was related to lower medication adherence. This too may reflect the desire of youth to fit in with their peers and not stand out because of their asthma, potentially resulting in their neglecting to take medications appropriately.

Explaining social network effects

Social support and social networks may affect asthma through a variety of pathways. For example, social networks are important sources of tangible support (ie, concrete assistance with tasks). This may take the form of providing rides to the doctor, watching siblings so that a parent can take a child with asthma to the doctor, or offering to pick up important medications from the pharmacy. The larger one’s social network, the more options one has to draw on for this type of help. These types of assistance with asthma management behaviors may help explain one way in which social networks can be beneficial for coping with asthma. Living with a chronic illness such as asthma can require a number of changes to daily routines, and it can be difficult for many families to balance asthma management with the other daily responsibilities in life. Hence, social networks may provide additional sources of support for managing with all these tasks.

Second, social networks may also provide tangible support in the form of knowledge and advice. For example, patients with asthma may learn new information from others with asthma, such as information about new medications or helpful sources of care for asthma. Patients with asthma may also learn from others different strategies for better managing their asthma (eg,
for remembering to take their medications) and may find others to be helpful role models for both daily management and responses to symptom exacerbations.

Another form of support offered by social networks is emotional support. In contrast to the concrete assistance of tangible support, emotional support refers to providing empathy and understanding for another person’s emotional reactions and feelings. This type of support could affect asthma outcomes in a number of ways. First, emotional support may help patients with asthma be more accepting of their illness. This may lead to more positive mental health states, with implications down the line for physical health. Second, support from others with respect to one’s emotional responses may help patients with asthma remain calm during times of symptom exacerbations. This in turn may facilitate appropriate implementation of asthma action plans and optimal responses to asthma symptoms. Third, support from others may increase positive emotional states and decrease negative emotional states more generally in patients with asthma. In turn, these emotional experiences could alter physiologic states in ways that have implications for asthma.

As we described above, social networks can sometimes have negative influences on asthma, particularly among youth. It is possible that youth with asthma are more susceptible to negative peer pressure because their asthma already makes them socially vulnerable. For example, if youth have activity limitations due to asthma that make them feel different and less accepted, they may be more likely to engage in maladaptive behaviors, such as smoking, to fit in or gain approval from peers. Thus, even if they are aware of the negative impact of such behaviors, knowledge alone may not be sufficient to drive behavior, particularly if there are competing pulls from peers that conflict with this knowledge.

**Family effects on asthma**

Evidence suggests that both the quality of family relationships and the psychosocial traits that family members possess affect asthma outcomes. Much of this research has focused on children with asthma and has investigated how family factors affect them. We will review evidence for links between family relationship quality and asthma, as well as links between parent traits, such as parental depression and stress, and childhood asthma.

**Family relationships**

The quality of relationships with family members affects not only a child’s psychologic well-being but also his or her physical well-being. For example, family relationships early in life predict the likelihood of children getting diagnosed with asthma years later. In a sample of children at risk for developing asthma, researchers measured parenting difficulties when infants were
3 weeks old. During home visits, clinicians assessed parenting difficulties by observing attitudes and behaviors parents exhibited toward their child, parents’ ability to regulate their child’s arousal and emotions, the supportiveness of parents’ relationship with each other, and the balance in the home between childcare and other demands. Children were then followed for several years to track the development of asthma. Greater parenting difficulties when an infant was 3 weeks old prospectively predicted a greater likelihood of that child being diagnosed with asthma, both by the age of 3 and by the age of 8 [47,48].

In addition, among children already diagnosed with asthma, family relationship quality contributes to morbidity and mortality. One classic example of this is a case-control study that recruited two groups of children hospitalized for asthma. One group consisted of children who died of asthma following hospital discharge. The second group was made up of children who did not die, despite having similar severity of illness. A number of psychologic and social factors distinguished these two groups, including parent-patient conflict and family dysfunction. Children in the group who died from asthma were more likely to have persistent and severe arguments with parents, as well as to have families with greater dysfunction (eg, intense marital conflict) [49]. Similar types of relationships were found with respect to asthma morbidity outcomes. Among a sample of children with asthma, those who reported receiving less support from their parents had more asthma symptoms and poorer daily pulmonary function [28].

*Parent characteristics*

The psychosocial characteristics of a parent can also affect asthma outcomes in a child. For example, higher levels of maternal depression have consistently been linked to childhood asthma. Shalowitz and colleagues [50] documented that parents who reported greater symptoms of depression had children who were more likely to use health care services and who experienced more severe asthma symptoms. Similarly, among a sample of children hospitalized for asthma, depression in parents was associated with a greater number of unscheduled physician visits as well as a greater number of hospitalizations for asthma in their children [51]. Longitudinal studies show similar patterns. Weil and colleagues [41] found that children of parents having clinically significant levels of mental health problems (including depression) at baseline had twice the rate of hospitalization for asthma during a 9-month follow-up period compared with children of parents without mental health problems. Inner-city mothers with high levels of depressive symptoms at baseline were 30% more likely than nondepressed mothers to report taking their children to the emergency department for asthma during the following 6 months [52]. These longitudinal data suggest that depression precedes poor asthma outcomes, rather than the opposite explanation—that having a child with poorer asthma causes parents to become more depressed.
Evidence linking parental depression to childhood asthma appears to be stronger for morbidity outcomes among those already diagnosed with asthma than for predicting asthma onset [53].

Greater parental stress also has been linked to increased asthma morbidity in children. For example, Shalowitz and colleagues [50] documented that caregivers with more negative life stressors were more likely to have children who used health care services and who experienced more severe asthma symptoms. Longitudinal studies show similar effects. Among a sample of children diagnosed with asthma, reports indicating greater life stress for parents predicted a greater likelihood of asthma hospitalization as well as poorer daily functioning in children over the following 9 months [41]. High levels of caregiver stress when infants were 2 to 3 months old predicted a higher likelihood of repeated wheezing in children by 14 months of age [54]. As with maternal depression, evidence suggests that parental stress may not predict asthma diagnosis [48,53]. However, parental stress may interact with family relationship problems to predict asthma. Parents who experienced a combination of both parenting difficulties (when the child was 3 weeks of age) and high stress at the end of pregnancy were five times more likely to have a child who developed asthma by the age of 3 compared with those without parenting difficulties (with or without high stress), and 2.5 times as likely to develop asthma compared with those with parenting difficulties but with low stress [55].

Explaining family effects

How does the psychologic state of one individual (a parent) come to affect asthma outcomes in another individual (the child)? One possibility is that the difficulties that children experience early in life may program their biological systems in a way that increases their vulnerability to asthma later in life. For example, difficulties bonding with parents may lead to insecure attachments and difficulties regulating emotions, which in turn may enhance the biological responses to stresses in children [56]. Certain family characteristics may also influence the amount of stress a child perceives. For example, family conflict or a poor quality family relationship can be a source of stress in and of itself. In addition, parental depression or stress may create stress for the child by affecting how parents interact with their child or because children are sensitive in picking up on the psychologic states of their parents.

Another possibility is that the family environment influences how children cope with events in their own lives. Coping refers to cognitive and behavioral efforts aimed at dealing with external demands from the environment [57]. One important type of coping strategy is to draw on close others to help you with your problems. A parent struggling with depression or significant life stressors may be less available to help a child deal with his or her problems. Hence, having low levels of family support may heighten
the impact of a stressor, given that these children will have more limited resources for getting help with their problems. In addition, children from difficult family circumstances may have parents who model maladaptive coping strategies. For example, children may observe parents with depression or stress struggling to cope with their own problems, and may attempt similar ineffective coping strategies for their problems. Or, such parents may use less effective coping strategies when parenting their child, leading children to have greater difficulty regulating their own emotional responses in daily life.

Another possibility is that family factors affect the health behaviors a child engages in, which in turn affects asthma morbidity. For example, parents who have high levels of depression or stress may be less available to supervise their child’s behaviors. This could lead to a greater influence of peers in shaping detrimental health behaviors, such as smoking. These parents may also have a more difficult time monitoring and ensuring their child’s compliance with asthma medications. This could mean that, among children whose parents are depressed or stressed, asthma is more likely to be improperly managed on a daily basis, leading to greater asthma morbidity over time.

Biological mechanisms

The above studies have linked social environment factors to clinical asthma outcomes. However, the question still remains of how the larger social environment gets “under the skin” to influence disease. Is there evidence that social environment factors are linked to biological processes implicated in asthma? In this section, we first briefly overview the types of inflammatory mechanisms relevant to asthma, and then address whether social factors are associated with these pathways. Other articles have provided broader overviews of biological systems implicated in biopsychosocial models of asthma [58–60].

Inflammatory pathways in asthma

One pathway to airway inflammation in asthma involves the activation of certain T helper cells, which in turn release cytokines that coordinate inflammatory responses. These cells, known as Th-2 cells, promote B cell proliferation and differentiation, leading to a humoral response involving antibody synthesis. For example, the Th-2 cytokines IL-4 and IL-13 bind to B cells, inducing them to synthesize and release IgE antibodies. IgE then binds to mast cells residing in the airways, causing them to degranulate and release allergic mediators, such as histamines and leukotrienes. Histamines and leukotrienes cause edema, smooth muscle constriction, and mucus production. A second type of inflammatory response is generated when Th-2 cells release IL-5. This cytokine recruits eosinophils into the airways, where they bring about inflammation and obstruction. Eosinophils also release mediators,
such as eosinophil cationic protein and major basic protein, which can bring about damage to airway cells, and leukotrienes, which cause edema and further bronchial constriction.

Social factors and inflammatory responses

At the neighborhood level, low SES has been linked to asthma-related inflammatory markers in children with asthma. In one study, adolescents diagnosed with persistent asthma were recruited from either low-SES or high-SES neighborhoods (based on the percentage of people living below poverty in each neighborhood). Peripheral blood was drawn from adolescents, and their cells were stimulated with a combination of phorbol myristate acetate and ionomycin to induce the production of cytokines. Adolescents with asthma from low-SES neighborhoods displayed significantly greater production of IL-5 compared with adolescents with asthma from high-SES neighborhoods, despite their cells having been exposed to an equivalent dose of mitogens [61]. In a subsequent study, children with asthma were recruited from a range of SES backgrounds. A linear relationship was found, such that as family SES decreased, production of IL-5, IL-13, and eosinophil counts all increased in children with asthma, but not among healthy children [62]. These findings suggest that low-SES children with asthma exhibit heightened inflammatory responses, and that the direction of these responses may help explain why low SES is linked to more severe exacerbations of asthma.

At the level of social networks and social support, one previously mentioned study [28] found that unlike family and neighborhood factors, peer support was not related to any of the biological variables investigated, including the production of cytokines implicated in asthma or eosinophil counts, in youth with asthma. These findings suggest that the link between peer support and biological processes in children with asthma is weak, perhaps consistent with the fact that the link between social support and clinical asthma outcomes is mixed. Another study examining the effect of social support on stress before and after examinations in high school students found that perceived social support decreased during examination time and that this decrease was accompanied by a decrease in natural killer cells [63]. However, this pattern for natural killer cells was found in both adolescents with asthma and in healthy adolescents, suggesting that social support may not activate immune pathways specific to asthma.

At the family level, recent evidence suggests that parent psychologic states are associated with child biological profiles. Higher levels of parental depression have been associated with eosinophil cationic protein (ECP), a substance released when eosinophils are activated. Specifically, greater parental depression at baseline predicted increases in ECP over the following 6 months in a sample of children with asthma and a sample of healthy children [64]. With respect to parental stress, higher levels of parental
perceived stress at baseline predicted greater increases over the following 6 months both in ECP as well as in stimulated production of IL-4 in these same samples of children [64]. Among young children, high levels of parental stress during the first 6 months of the child’s life predicted higher IgE levels at 2 years of age, as well as an increased proliferation of children’s lymphocytes after in vitro exposure to selected allergens [65]. These findings suggest that poorer parent mental health is associated with inflammatory profiles in children in a direction detrimental to asthma.

In earlier sections, we hypothesized that one reason why larger social environmental factors influence health outcomes is because environmental factors, such as low SES and poor family relationships, affect the stress that an individual experiences. In turn, clinical evidence indicates individuals who experience greater stress also are at risk for poorer asthma outcomes [35,66,67]. Recent evidence corroborates this clinical data, suggesting that stress affects inflammatory processes of individuals with asthma. For example, in one study, college students with asthma were tested during periods of high stress (final examination period) and during periods of low stress (no major examination) [68]. Each time, participants inhaled increasing dosages of allergens to which they were sensitized (ragweed, cat, or dust mite) until their pulmonary functioning declined by 20% or more. There was evidence of a greater immune response to this challenge during times of stress. During final examinations, the allergen challenge elicited greater numbers of eosinophils in both sputum and blood compared with periods outside of examination time. A parallel finding emerged for in vitro production of IL-5 in sputum treated with phytohemagglutinin.

In a separate series of studies, high school students were studied before an examination (baseline period of low stress) and after examinations (high-stress period), and their peripheral blood cells were stimulated in vitro with various mitogens. In one study, students with asthma had greater production of IL-5 postexamination compared with students who were healthy. In contrast, there were no group differences in IL-5 production at baseline. This suggests that under conditions of low stress, individuals with asthma do not differ from healthy individuals in their responsiveness to mitogens, but that periods of stress heighten the responsiveness of Th-2 immune cells to mitogens in individuals with asthma [69]. A second study from this group documented that examination stress was associated with reduced production of the Th-1 cytokines IFN-\(\gamma\) and IL-2, but increased production of the proinflammatory cytokine IL-6 (argued by this group to represent Th-2) across both a sample of students with asthma and a sample of healthy students [70]. Collectively, these studies suggest that, among patients with asthma, stress can amplify the Th-2 cytokine response to asthma triggers and mitogens. Over time, such an inflammatory pattern could lead to more frequent or severe symptoms of asthma.

Taken together, the studies reviewed in this section provide intriguing evidence that the larger social environment—in particular at the family and
neighborhood levels—can alter biological systems in individuals. This link between the social environment and biology is important to provide plausible explanations for how it is that social environments come to influence the course of diseases. With additional empiric evidence from future studies, researchers can begin to develop more comprehensive models of how larger social factors affect individuals psychologically and behaviorally, and in turn what the biological and long-term health implications of these effects are.

Summary

In this article, we addressed the question of whether the social environment affects the onset or course of asthma. We reviewed evidence showing that neighborhood-level factors, such as low SES and community violence, are associated with greater asthma morbidity. In addition, family-level factors, such as poor quality family relationships, parental depression, and parental stress, are associated with poorer asthma outcomes. In contrast, peer-level factors, such as social support, were more mixed in their association with asthma, with some studies finding that support is beneficial for asthma, and others finding no relationship or even detrimental effects of peers on asthma. Longitudinal studies indicate that neighborhood and family social factors precede asthma, rather than being a consequence of asthma. The strongest evidence exists for social factors predicting morbidity among those already diagnosed with asthma, with evidence being more mixed for social factors predicting the development of asthma. Social factors likely operate via direct effects on physiologic systems, as well as by changing health behaviors in individuals with asthma. In sum, while exposure to factors in the physical environment has long been recognized as contributing to asthma, the studies reviewed in this article highlight the importance of also considering social exposures in asthma. To push the field forward in developing more comprehensive models of asthma, the concept of environmental exposures in asthma needs to be more broadly defined. Exposures, both physical and social, affect asthma in significant ways.

References


Asthma in the Inner City and the Indoor Environment

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Inner-city residents continue to suffer disproportionate asthma morbidity despite recent progress in reducing asthma morbidity and mortality in other strata of the United States population. Although many factors are likely responsible for these disparities, studies conducted over the past decade indicate that the indoor environment is a strong contributor to poor asthma control and asthma-related health care use in inner-city populations. The term “inner city” generally refers to impoverished urban neighborhoods where housing is often very old and dilapidated, so that certain indoor exposures are more common and occur in higher concentrations than in suburban communities [1]. Identification of “asthmagenic” indoor exposures has paved the way for the development of intervention strategies aimed at reducing asthma morbidity, principally by reducing these

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\text{doi:10.1016/j.iac.2008.03.004}
\text{immunology.theclinics.com} \]
exposures. This article reviews the growing body of evidence that certain indoor environmental exposures contribute to the burden of asthma in the inner city.

The major categories of indoor exposures include allergens and other biologics, such as endotoxin, as well as pollutants. The major indoor allergens include those associated with dust mites, cats, dogs, mice, rats, cockroaches, and molds. Important indoor air pollutants include particulate matter (PM), nitrogen dioxide (NO₂), secondhand tobacco smoke, and ozone.

**Indoor allergens and endotoxin**

*Overview*

Allergic sensitization is an important risk factor for asthma for both children and adults. One recent study that included children and adults estimated the population-attributable risk for allergic sensitization to be 56%. In other words, more than half of asthma cases in the United States can be attributed to allergic sensitization [2]. In the pediatric population, about 80% of school-age children with asthma have evidence of allergic sensitization to at least one common environmental allergen [3,4]. Allergic sensitization to the predominant allergen in a community confers a 4- to 20-fold increase in the risk of asthma [5–7], suggesting a causal relationship between allergen exposure and the development of asthma. Moreover, populations with more poorly controlled asthma have higher prevalence rates of sensitization than populations with well-controlled asthma. In one recent inner-city study of children with poorly controlled asthma, a staggering 94% of children had evidence of allergic sensitization [8], highlighting the potential importance of allergic sensitization as a risk factor for poorly controlled asthma. Studies have also clearly demonstrated that exposure can lead to both acute and chronic symptoms in sensitized patients with asthma [4,9–13]. Although seasonal allergens are known triggers of asthma, overall exposure to indoor allergens may be greater given the substantial amount of time spent indoors as well as the year-round presence of many indoor allergens. In addition, among inner-city children with asthma, sensitivity to indoor allergens is more prevalent than sensitivity to outdoor allergens, underscoring the relevance of indoor allergen exposure in this population [14].

Although all of the major allergens can be found in inner-city homes, the distribution of allergens depends somewhat on the geographic region of the inner city [8,15,16]. For example, the dust mite is the predominant allergen in inner-city homes of southern and northwestern United States. In contrast, pest allergens, such as rodent and cockroach allergens, are the predominant allergens in northeastern inner-city homes where dust mite allergens are less common. Some of these regional differences in allergen ecology appear to be due to differences in climate and housing stock. As such, it is important to understand which allergens are most important in a given geographic area.
so that appropriate allergy testing can be performed, and tailored environmental control recommendations can be provided to patients.

**Rodent allergens**

Mice and rats excrete urinary allergens that are carried on small particles that readily become airborne [17–19]. The allergens are pheromone-binding proteins that are thought to have a role in mating practices [20] and are excreted in very large quantities in the urine. Although these allergens have long been known to cause occupational asthma, their role in nonoccupational asthma has only recently been described [12,21]. In fact, in some inner cities, mouse allergen appears to be an important contributor to asthma morbidity.

The domestic house mouse (*Mus musculus*) is very common, particularly in urban areas where multifamily dwellings and poorly maintained housing are common [16,22]. Mouse allergen can be found in virtually all inner-city homes, and one study found detectable airborne mouse allergen in 84% of bedrooms of inner-city children with asthma [23]. Airborne mouse allergen levels in as many as 25% of inner-city homes are similar to levels measured in occupational settings, where mouse allergen is a known cause of asthma symptoms. Mouse allergen is surprisingly prevalent in suburban communities as well, with as many as 75% of middle-class, suburban households having detectable mouse allergen levels in settled dust samples [16,24]. However, the levels in these suburban homes are 100-fold lower than the levels observed in inner-city settings. For example, the median settled-dust mouse allergen level in inner-city bedrooms is approximately 2.5 µg/g as compared with 0.02 µg/g in suburban bedrooms. Overall, as many as 75% of homes in inner cities may have clinically relevant levels of mouse allergen [12].

Sensitization to mice is also common, with 18% to 28% of inner-city children with asthma having evidence of allergic sensitization to mice [8,12,21]. Since most of these children are also exposed to clinically relevant levels of mouse allergen, more than 20% of inner-city children with asthma may be at risk for increased morbidity from mouse allergen exposure.

Recent studies have linked exposure to mouse allergen to poorer asthma control and an increased risk of asthma-related health care use among mouse-sensitized, inner-city children with asthma [10,12]. In a Baltimore study, mouse-sensitized children with more than 0.5 µg/g of mouse allergen in bedroom settled dust had more symptom days and more days of rescue medication use than children who either were nonsensitized or had lower levels of mouse allergen in their bedrooms. The sensitized and more highly exposed children were also more likely to visit the emergency department or be hospitalized for asthma than children who were either not sensitized or were exposed to lower levels of mouse allergen [12].

Any patient who reports mouse sightings or evidence of mice, such as droppings, is very likely to be exposed to significant levels of mouse allergen.
in the home [22–24]. However, as with cockroach allergen, patients and families may be reluctant to admit a rodent infestation, so that a negative history is not a good predictor of lack of exposure. In addition, substantial levels of mouse allergen can be found in homes with little or no evidence of infestation, because mice nest in hidden spaces and are active at night.

Reducing exposure to mouse allergen is feasible, but can be difficult. Although several studies have found an association between the presence of a cat and lower mouse allergen levels [22,23,25], acquisition of a cat as a means of lowering mouse allergen levels has not been studied. In addition, acquisition of a cat should not be recommended as a means of reducing mouse allergen levels in patients who are allergic to both mice and cats. Integrated pest management is the best approach and includes a combination of extermination, vigorous cleaning, meticulous disposal of food remains, and sealing of holes and cracks in walls, doors, and ceilings. Using this approach, the allergen source is eliminated, the allergen reservoirs are cleaned up, and reinestation is discouraged. In one study, integrated pest management resulted in a 75% reduction in mouse allergen levels in settled dust, while levels increased in the control group [26]. Although no studies have been conducted to determine the impact of mouse allergen reduction on asthma, the evidence to date indicates that reduction of exposure has the potential to improve asthma control and prevent asthma-related morbidity.

Rats are also common in urban areas and, although they typically do not venture indoors, rat allergen has been found in 33% of inner-city homes. In one multicenter study, 21% of inner-city children with asthma were sensitized to rats, and the children who were sensitized and exposed to rat allergen in their homes were at greater risk for asthma-related hospitalization and unscheduled medical visits than children who either were not sensitized or not exposed [13]. No published studies have examined methods of reducing household rat allergen, but a reasonable approach would include sealing holes and cracks in the home’s structure, vigorous cleaning to remove reservoir allergen, and extermination.

Cockroach allergen

The two most common cockroaches found in United States homes are the German cockroach (Blatella germanica) and the American cockroach (Periplaneta americana). Cockroach allergens are carried on relatively large particles (10–40 μm) that quickly settle to dependent surfaces so that the allergens are easiest to detect in settled dust samples, but very difficult to detect in air samples. Multiple allergens from each of these cockroach species have been characterized, but inner-city asthma studies have primarily focused on the German cockroach (Bla g) allergens. Several studies have found that at least half of inner-city homes have clinically relevant levels of cockroach allergen [4,8]. Although as many as 30% of suburban, middle-class homes also contain detectable levels of cockroach allergen, the levels in
suburban homes are much lower than levels found in inner-city homes [15,27]. For example, approximately half of homes in the inner city have a Bla g 1 level greater than 8 U/g, a level associated with asthma morbidity, but only 10% to 12% of suburban homes have levels that exceed this threshold [27,28].

In inner-city populations, 30% to 70% of children with asthma are sensitized to cockroaches [8,29], and in suburban populations, sensitization rates are about 21% [27]. Cockroach allergen has also been directly linked to poorer asthma outcomes in inner-city children with asthma, including asthma-related health care use [4,8]. In the National Cooperative Inner-City Asthma Study, cockroach-sensitized children with more than 8 U/g of cockroach allergen in their bedrooms had greater morbidity than either nonsensitized or less exposed children [4]. These findings were replicated in the Inner-City Asthma Study for exposure to cockroach allergen levels greater than 2 U/g [8], suggesting that levels below 8 U/g may be sufficient to trigger asthma symptoms.

In light of these findings, it is important to assess risk of exposure in sensitized patients and make recommendations for reducing cockroach allergen exposure. Although patient report of cockroach infestation is a good indicator of significant levels of cockroach allergen exposure [15], one cannot be reassured that a patient is not exposed to significant levels of allergen if they fail to report cockroach infestation. Patients may be reluctant to admit pest infestation, and homes without evidence of active infestation often contain substantial levels of the allergen.

Substantial reductions in cockroach allergen levels can be achieved using an integrated pest management approach. Several studies have demonstrated that a combination of extermination, vigorous cleaning aimed at reducing reservoir allergen, and meticulous care in disposing of food remains can result in 80% to 90% reductions in cockroach allergen levels [30,31], although not all studies have had this degree of success [32]. One recent study pointed out the importance of using certain pest management techniques, including use of traps, to monitor and direct treatments. This same study showed that methods used by some pest management companies may be inadequate to achieve substantial and lasting reductions in allergen levels [33]. It remains unknown if cockroach allergen reduction alone has a clinical impact. However, the strong evidence that cockroach allergen exposure is linked with asthma morbidity supports recommending an integrated pest management approach to reduce exposure in cockroach-sensitized patients with asthma.

Pet allergens

Unlike cockroach allergens, cat and dog allergens are carried on small particles that remain airborne and are very adherent to surfaces and clothing [34]. These properties lead to widespread distribution, such that cat and dog
Allergen can even be detected in public buildings, such as schools [35,36]. Allergen is brought to school on the clothing of children with pets at home, and the highest airborne allergen levels occur around the desks of those children with pets [35]. Cat and dog allergens are obviously found in homes with these pets, but the allergens can also be found in homes without pets, though the concentrations are typically 10 to 1000 times lower than homes with a pet [37,38].

The practice of pet keeping occurs across almost all communities in the United States, so that, in general, studies of pet allergen exposure have not focused explicitly on inner-city environments. However, a few inner-city studies, particularly recent multicenter inner-city asthma studies, provide some insight into levels of pet allergens and their potential impact on asthma in these communities. These studies have found that there is somewhat less pet ownership in inner-city homes than in suburban homes [39]. Approximately 15% of inner-city families report having a dog, and approximately 13% to 25% report having a cat [8,40], while more than half of suburban families keep pets [39,41]. Not surprisingly, cat and dog allergen levels tend to be lower in inner-city homes than in suburban homes [39]. Sensitization to cats and dogs is also common in inner-city populations with asthma. In the Inner-City Asthma Study, 44% of children were sensitized to cats and 21% to dogs [8], and the prevalence rates of sensitization in suburban or non–inner-city populations range from 50% to 80% for cats and 20% to 30% for dogs [3,39].

For both cat and dog allergens, considerable evidence supports a relationship between allergen exposure and exacerbation of asthma in sensitized individuals. Epidemiologic studies have demonstrated an increased risk of exacerbations among patients who are both sensitized and highly exposed to cat allergen [8,42]. In addition, allergen challenge studies demonstrate that cat-sensitized asthmatics develop asthma symptoms and decreased lung function in response to airborne cat allergen, even at low levels [37,43,44].

An atopic child with asthma who is sensitized to cat or dog allergen should not live with the respective pet in the home. Pet removal reduces airway responsiveness in those with pet allergic asthma [45]. Once a pet has been removed, allergen levels in settled dust fall in 4 to 6 months to those seen in homes without cats [46]. Levels fall more rapidly if extensive environmental controls are undertaken, such as removal of carpets, upholstered furniture, and other reservoirs, as well as thorough and repeated cleaning. Cat allergen may persist in mattresses for years after a cat has been removed from a home [47], so the purchase of new bedding or impermeable encasements is also recommended. Because so many sensitized patients are unwilling to remove a pet, many compromise measures have been suggested. The use of high-efficiency particulate air (HEPA) filters and vacuum cleaners results in short-term reductions in airborne cat and dog allergen levels, but no change in settled dust allergen concentrations [48–52]. No studies
to date show an effect of air filters on disease activity [46], although one study demonstrated a reduction in airway responsiveness, without change in any other clinical measure [53].

**Dust mite allergens**

The major dust mite allergens are carried on relatively large particles (10–30 μm) that only briefly remain airborne [54]. The mites infest fabrics and are not particularly mobile, and disturbance is required to detect the allergens in the air. The distribution of house dust mite allergens varies widely among different homes [55,56], with highest concentrations found in the bedroom, especially in the bed. Higher allergen levels are associated with increased moisture, such as in damp houses and basement bedrooms [57].

Because dust mites require higher relative humidity for survival, there are striking geographic differences in dust mite allergen levels. For example, multicenter inner-city asthma studies have found that the highest dust mite allergen levels are found in southern cities, such as Dallas, and northwestern cities, such as Seattle, where two thirds of inner-city homes have clinically relevant levels of mite allergen [8]. In contrast, only 8% to 20% of inner-city homes in New York, Chicago, and Baltimore have clinically relevant dust mite allergen levels. There also appears to be differences between suburban and inner-city homes in the same region of the United States. For example, dust mite allergen levels are approximately five-fold higher in suburban Maryland homes than in inner-city Baltimore homes. The median bedroom dust mite allergen level is 66 ng/g in inner-city Baltimore homes [58], but is 360 ng/g in suburban Maryland homes [59]. Because of these regional and community differences in dust mite allergen levels, few published studies have focused explicitly on dust mite allergen and asthma in inner-city communities.

However, based on all studies to date, the 2000 Institute of Medicine Report concluded that there are causal relationships between (1) dust mite allergen exposure and the development of asthma in susceptible children and (2) exposure and asthma exacerbations in sensitized individuals [60]. The evidence cited includes studies in various countries demonstrating an association between dust mite sensitization and asthma (with odds ratios of 6 or more) [5], bronchial provocation experiments showing allergic response [61], and studies of clinical outcomes after mite allergen avoidance [62–69].

Evidence supports dust mite allergen control measures as a reasonable approach to improving asthma in children, though whether to recommend the practices on a larger scale remains controversial. The most effective method of control is the use of allergen-proof encasings fitted to the mattress and pillow [63,70]. Of more than a dozen clinical trials of allergen-proof encasings, seven have demonstrated a reduction in mite allergen and a clinical effect [64–69]. Dust mite covers are available by mail or in retail stores, are
breathable and comfortable, and exclude nearly 100% of particles carrying mite allergen [71]. Although prior studies have found that allergen-proof bed covers can reduce mite allergen levels and improve clinical outcomes in selected populations, one recent study of over 1100 adults suggests that providing encasings to all patients with asthma may not be an effective public health intervention [72]. Washing sheets, pillowcases, blankets, and mattress pads at least weekly in warm water with detergent and with 8- to 10-minute cycles removes virtually all mite allergen [73]. Dry cleaning [74] and prolonged tumble drying [75] effectively kill mites, but are less effective at removing allergens. Vacuum cleaning reduces the bulk of household dust and reduces the overall exposure burden, but does not change the concentration of mite allergen in settled dust [76]. Second line measures for which there is evidence of mite allergen reduction include removal of wall-to-wall carpeting [77] and steam cleaning [78]. Other measures without supporting evidence include relocation of the bedroom [78] and application of acaricides [79]. The evidence surrounding dehumidifiers is inconsistent, with some studies showing a reduction in mite allergen levels [80], and others not [81].

**Mold**

Mold, a saprophytic fungus, requires moisture, elevated temperatures, and nutrients to grow. These conditions are often found in homes. Mold spores are small (2–10 μm), and therefore can remain airborne for extend periods. Hundreds of species of mold can be found indoors. Although there has been a great deal of interest in mold exposure and its impact on respiratory health, studies have been hampered by the complexity of the assessment of mold exposure. Molds can be quantified by measuring spore counts, culturable spores, allergens, or fungal products, and it is not entirely clear which method is best for examining the impact of mold exposure on asthma. In addition, molds can cause adverse health effects through multiple mechanisms, adding to the challenge of studying the impact of mold exposure on asthma.

Despite these challenges, a growing body of evidence shows that allergic responses to inhaled mold allergens do result in increased asthma symptoms. Most of these published studies focus on the role of outdoor mold exposure and asthma symptoms, but more recent studies have focused on indoor mold exposure. The best-studied mold in asthma is Alternaria. Exposure to outdoor Alternaria has been associated with asthma symptoms, bronchial hyperresponsiveness, and severe asthma in sensitized individuals in several reports [82–85]. In a recent study, levels of indoor Alternaria were associated with an increased risk of asthma symptoms [86].

Mold exposure has been comprehensively assessed in only a few inner-city asthma studies. In the Inner-City Asthma Study, indoor culturable airborne fungi levels were correlated with outdoor levels, underscoring the importance of considering outdoor levels when assessing the relative degree
of indoor fungal exposure [87]. Homes with dampness, a cat, and cockroach infestation were more likely to have indoor fungal levels that were higher than outdoor fungal levels.

The National Academy of Sciences review of asthma and indoor air exposures [60] concluded that there is sufficient evidence of an association between fungal exposure and symptom exacerbation in sensitized asthmatics. The National Academy of Sciences also concluded that evidence is inadequate or insufficient to determine whether there is an association between fungal exposures and the development of asthma. In addition, a large body of literature suggests that damp housing, assessed by evidence of water damage or excessive moisture, is associated with respiratory symptoms and asthma severity [88]. While it is often inferred from this literature that mold is the likely culprit, damp housing is potentially a surrogate for increased pests and their allergens as well as bacteria, viruses, and fungi [88,89].

Patients with asthma should be evaluated for mold sensitization by skin testing or specific IgE testing and, if indoor fungal sources are present, steps should be taken to remove the indoor mold. Although detailed information about abatement strategies are beyond the scope of this article, information about abatement can be found in the 2004 Institute of Medicine’s report, “Damp Indoor Spaces and Health” [89].

**Allergen abatement recommendations in clinical care**

In clinical practice, each patient must be assessed for allergic sensitization using skin testing or serum-specific IgE tests. In fact, many inner-city asthma patients have multiple allergic sensitivities and identification of the specific sensitivities will guide exposure-reduction recommendations. For example, a patient with dust mite and cockroach sensitization should be counseled to concentrate on environmental-control practices aimed at reducing exposure to these allergens, while another patient with cat and mouse sensitizations should concentrate on implementing measures to reduce exposure to these allergens. In general, strategies aimed at reducing a single allergen [32] have been less successful than multimodal interventions in reducing exposures and, consequently, improving asthma control [90,91]. The most recent National Asthma Education and Prevention Program guidelines also support a multimodal approach over a single allergen approach as an integral part of asthma management [92].

**Endotoxin**

Endotoxin is a proinflammatory lipopolysaccharide that makes up the outer membrane of gram-negative bacteria and produces reversible airway inflammation in animal models and human challenge studies [93–95]. Though some epidemiologic evidence in early life suggests that endotoxin exposure may protect against the development of allergic disease [96,97], other studies have found higher levels of endotoxin in homes of children
with asthma compared with control homes, suggesting that endotoxin may be a risk factor for the development of asthma [98,99]. In some farming communities, high indoor endotoxin exposure is associated with a decreased risk of wheezing and atopic asthma [96]. However, endotoxin levels in these communities may be several-fold higher than levels seen in nonfarming environments, including the inner city. In fact, several studies that have focused on nonfarming communities have reported seemingly contradictory findings. These studies demonstrated a link between increasing endotoxin concentrations and increased prevalence of wheeze in individuals at risk of developing asthma [94,100–102]. Perzanowski and colleagues specifically studied an inner-city birth cohort and demonstrated that children in homes with higher endotoxin concentration were more likely to wheeze at age 2 years (odds ratio 1.34; 95% CI 1.01–1.78) compared with children with lower endotoxin concentrations. Taken together, it appears that endotoxin is a risk factor for wheeze in nonfarming communities, including the inner city, but may protect against wheeze in early-life exposures at the highest levels seen in farming communities.

Many studies have shown that, among subjects with asthma, domestic endotoxin exposure is associated with greater asthma severity and increased morbidity, as measured by symptoms, lung function, and medication use [103–106]. Although these findings have not been replicated in inner-city populations, endotoxin levels in inner-city homes are comparable to those in other nonfarming communities where endotoxin has been associated with adverse asthma outcomes [102,107]. However, endotoxin levels in lower-income homes may be higher than those in higher-income homes. For example, in a study conducted in Denver, Colorado, lower-income homes had higher endotoxin concentrations compared with those in higher-income homes [107]. This finding may suggest that endotoxin has some link to increased asthma morbidity in lower socioeconomic homes, though further research is needed to address this hypothesis.

Despite the evidence supporting a link between endotoxin exposure and asthma morbidity, no intervention studies specifically evaluating the effectiveness of reducing endotoxin concentration on asthma morbidity have been performed. However, in a prospective randomized controlled trial, a home remediation strategy aimed at moisture reduction noted a decrease in endotoxin concentrations as well as asthma symptom days and healthcare use [108]. Thus, efforts at reducing endotoxin may eventually be shown to reduce asthma morbidity. However, evidence is now insufficient to support that practice.

**Indoor air pollution**

Indoor air pollution is a complex mixture of pollutants migrating indoors from outdoor air and pollutants generated by unique sources indoors. Even though Americans spend nearly 90% of their time indoors [109], most
scientific investigation of pollutant effects on asthma has focused on outdoor rather than indoor air pollution. Exposure to outdoor air pollutants has been associated with increased airway reactivity, asthma exacerbations, respiratory symptoms, and decreased lung function [110–113]. For some pollutants, indoor air concentrations can greatly exceed outdoor air concentrations [58,114]. Although the link between asthma and indoor air pollutants has not yet been thoroughly studied for all pollutants, research to date suggests that indoor air pollution may play a significant role in asthma morbidity. We summarize the findings of the effects of indoor air pollutants, including ozone, particulate matter, NO₂, and secondhand tobacco smoke, on asthma morbidity.

**Particulate matter**

PM consists of solid and liquid particles suspended in the air. For outdoor air, the Environmental Protection Agency regulates particulate concentrations through the National Ambient Air Quality Standards. These standards define acceptable outdoor particulate concentrations based on particle size, and outdoor air quality is monitored through a network of national monitoring sites. Until recently, one standards applied to particles with an aerodynamic diameter of less than 2.5 μm (PM₂.₅) and another applied to particles with an aerodynamic diameter of less than 10 μm (PM₁₀). However, in the latest update, PM₂.₅ standards were made more stringent and the PM₁₀ annual standard was repealed with a new goal of implementing standards for the coarse PM fraction, defined as particles measuring from 2.5 to 10 μm (PM₂.₅₋₁₀). One reason that regulations for PM₂.₅₋₁₀ may supplant those for PM₁₀ is that PM₂.₅₋₁₀ does not overlap with the PM₂.₅ measurement while the majority of PM₁₀ is accounted for by particles that are smaller than 2.5 μm in diameter. Individual consideration of acceptable concentrations of both fine PM (PM₂.₅) and coarse PM (PM₂.₅₋₁₀) is important as particles of different sizes have different sources, composition, and deposition properties. Studies have consistently shown an association between elevated outdoor concentrations of PM and asthma morbidity, and most of these have focused on populations living in major cities [115–119].

Activities associated with elevated indoor PM include smoking, as well as cleaning (eg, sweeping) and cooking (eg, use of the stove, frying foods) [120,121]. Cigarette smoking is a substantial contributor to indoor PM as one study found that smoking households had average PM₂.₅ and PM₁₀ concentrations that were 33 to 54 μg/m³ greater than those of nonsmoking households, with each cigarette smoked adding 1.0 μg/m³ to indoor PM concentrations [58]. The observation that smoking is a major source of indoor PM is a consistent observation across numerous studies [120,122,123].

A few studies have examined the health effects of indoor PM exposure in study populations living near large cities, though it is not clear from the
reports how many of the studied homes would be considered “inner city” [119,124,125]. These studies suggest that there is a relationship between indoor PM exposure and asthma morbidity. Indoor PM has been shown to be inversely associated with lung function among children with asthma [119,124], and PM$_{2.5}$ originating from indoor sources may be more potent per unit mass in decreasing lung function compared with outdoor-derived PM [124]. Furthermore, among asthmatic children not taking inhaled corticosteroids, increases in exposure to indoor fine PM has been associated with increases in exhaled nitric oxide levels, suggesting that indoor PM may stimulate airway inflammation [124]. While these studies suggest that PM is associated with decreased lung function and increased airway inflammation, the studies to date have been relatively small and have not yet clarified whether or not there is an association with asthma exacerbations and acute health care encounters. Ultimately, studies examining the effect of PM reduction are necessary to more fully understand the potential impact of indoor PM on asthma. Although no intervention studies have explicitly targeted indoor PM, a handful of studies have incorporated HEPA filters as part of multifaceted approaches to environmental modification. These studies have demonstrated that HEPA filters are effective in lowering the concentration of indoor PM in homes of children with asthma and that, as part of a multimodality intervention to improve the home environment, they may have a modest effect in reducing asthma morbidity [91,126]. Studies that isolate the independent effect of PM reduction, and that evaluate the effectiveness of comprehensive PM reduction strategies, including source modification, ventilation, and HEPA filter placement, are still needed to better elucidate the potential benefit of PM reduction as a strategy to improving asthma health.

 Nitrogen dioxide

NO$_2$, a common ambient air pollutant, is a product of high temperature combustion. There are many potential indoor sources of NO$_2$, including gas stoves, space heaters, furnaces, and fireplaces [127,128]. The National Cooperative Inner-City Asthma Study conducted in eight inner-city areas in the United States showed a link between higher levels of indoor NO$_2$ and increased asthma symptoms in children and decreased peak flows [129]. Similarly, Hansel and colleagues [130] showed a consistent association between higher NO$_2$ concentrations and increased asthma symptoms in preschool children in inner-city Baltimore. Meanwhile, another study found that indoor NO$_2$ exposure was associated with chest tightness and wheezing, but only in individuals living in multifamily housing units. Since this living arrangement is an indicator of lower socioeconomic status, this finding highlights the complex interaction of this exposure with poverty [131].

NO$_2$ may be a particular problem in the inner city where many households use gas stoves and, perhaps as indications of limited financial
resources, many of these stoves are unvented [40,58] and used for prolonged periods as a source of household heat [130]. In fact, studies assessing NO\textsubscript{2} concentrations in inner-city homes have demonstrated that they can be higher than those generally reported in other residential settings in the United States [40,58,129,132]. Since some evidence suggests low levels of NO\textsubscript{2} are not harmful but that higher levels of exposure are linked to increased asthma morbidity [129], inner-city populations may be uniquely at risk for adverse effects of indoor NO\textsubscript{2}.

When high NO\textsubscript{2} concentrations are suspected, general control strategies can include source modification and ventilation. A randomized controlled trial studying the effects of reducing NO\textsubscript{2} in schools by replacing unflued gas heaters with flued gas or electric heaters showed a lower indoor NO\textsubscript{2} concentration in schools receiving the intervention compared with schools that retained the unflued gas heaters (15.5 ppb versus 47.0 ppb, \( P < .001 \)) with a concordant lower risk of asthma symptoms (difficulty breathing [relative risk 0.41; 95% CI 0.07–0.98], chest tightness [relative risk 0.45; 95% CI 0.25–0.81] and asthma attacks [relative risk 0.39; 95% CI 0.17–0.93]) in schoolchildren [133]. While not an intervention study, observations by Kattan and colleagues [129] found a protective effect of stove vents on indoor NO\textsubscript{2} levels that approached statistical significance. Though definitive intervention studies in inner-city homes are warranted, we would recommend that individuals with asthma, if afforded the opportunity to choose housing, choose residences without gas stoves and heaters. For those who already have these appliances, they should be cautioned at least about the need for proper venting of the exhaust gases.

Secondhand smoke

Secondhand smoke is involuntarily inhaled tobacco smoke that contains particles and gases generated by the combustion of tobacco, paper, and additives [134]. The most recent and most comprehensive review of secondhand smoke, smoking, and asthma was published in the 2006 Report of the US Surgeon General on the Health Consequences of Involuntary Exposure to Tobacco Smoke. The surgeon general concluded that there is sufficient evidence for a causal relationship between secondhand smoke exposure from parental smoking and the onset of wheeze illness in early childhood and that there is suggestive evidence of a causal relationship between secondhand smoke exposure from parental smoking and the onset of childhood asthma [134]. The surgeon general’s report also concluded that clear evidence demonstrates that secondhand smoke exposure makes childhood asthma more severe clinically. With respect to adults, the report concluded that the evidence is suggestive but not sufficient to infer a causal relationship between secondhand smoke exposure and acute respiratory symptoms, including cough, wheeze, chest tightness, and difficulty breathing, among persons with asthma [134]. There is published evidence, however, that
asthma health outcomes are worse in adults with secondhand smoke, when exposure is measured directly using nicotine badges and hair measures of cotinine and nicotine [135]. This topic is reviewed in depth in another article by Eisner elsewhere in this issue.

The prevalence of tobacco use in some urban families is alarmingly high. Data from inner-city neighborhoods in Baltimore, for example, indicate that more than 55% of homes of young asthmatics have at least one active smoker in the home [40,136]. While most exposure for young children is typically in the child’s own home, 34% of children who live in nonsmoking homes may nevertheless spend time in other homes (eg, grandparents) where smoking is reported, according to another study [137].

The surgeon general’s report states that “eliminating smoking in indoor spaces fully protects nonsmokers from exposure to secondhand smoke. Separating smokers from nonsmokers, cleaning the air, and ventilating buildings cannot eliminate exposures of nonsmokers to secondhand smoke” [134]. There is substantial evidence suggesting that secondhand smoke avoidance should result in improved asthma outcomes. However, studies examining the effectiveness of interventions to reduce secondhand smoke exposure show relatively insignificant effects of interventions on the smoking patterns of those who smoke near children with asthma [138,139]. There have not, to our knowledge, been clinical trials of secondhand smoke reduction in adults with asthma [134]. Recently published asthma guidelines recommend that patients who are active smokers be referred to smoking cessation programs and that all patients with asthma be counseled concerning the negative effects of smoking and secondhand smoke [92]. Substantial evidence suggests that secondhand smoke avoidance can result in improved asthma outcomes. However, effectiveness of home intervention studies attempting to reduce secondhand smoke exposure show relatively small differences in the subsequent number of cigarettes smoked in the home [138,139]. Evidence from studies of restaurants, hospitals, and other public places indicates that bans on indoor smoking can substantially reduce secondhand smoke exposure even with incomplete compliance [140]. To our knowledge, there is no evidence regarding the degree of reduction in secondhand smoke exposure that can be achieved through ventilation and air cleaning in the homes of smokers who continue to smoke indoors.

Ozone

Ambient ozone is the main contributor to indoor ozone concentrations. Therefore, indoor concentrations of ozone are directly related to outdoor concentrations and show significant seasonal variability [58]. Indoor sources of ozone are uncommon, but include ionizers or ozone generators, which are sold as air freshening or air cleaning devices, and xerographic copy machines found in offices, schools, and some home offices [60]. Epidemiologic studies of ambient ozone and experimental studies show a significant
association with asthma-related morbidity, including increases in symptoms, health care use, and airway inflammation and decreases in lung function [141–145]. The effect of indoor ozone levels on asthma morbidity has not been well studied. Similarly, the benefits of indoor ozone reduction on asthma morbidity are unknown. However, because ozone is a highly reactive gas, concentrations are generally much lower indoors relative to outdoors, even in peak ozone season, and evidence suggests that indoor ozone levels may be reduced by keeping windows and doors closed [146]. Furthermore, ozone-generating “air cleaners,” “air filters,” “air purifiers,” and similar equipment should be avoided in the home of patients with asthma.

Summary

There is growing recognition of the importance of the indoor environment in the asthma burden in inner cities. Certain indoor allergens and pollutants are found in higher concentrations in inner-city homes, suggesting that any impact that these exposures have on asthma may be more pronounced in inner-city populations. Mouse and cockroach allergens in particular are prominent allergens in inner-city environments and contribute to asthma morbidity. Among indoor pollutants, PM, secondhand smoke, and NO₂ in particular, are found in higher concentrations in inner-city homes than in non–inner-city homes and are also known to contribute to asthma morbidity. Because multiple exposures are found in any given inner-city home, it is critical to understand how allergens, biologic pollutants, such as endotoxin, and pollutants interact. More detailed epidemiologic studies comprehensively evaluating the indoor pollutants and allergen exposures are warranted to investigate this interaction further. In addition to this line of investigation, more work still needs to be done to develop and evaluate interventions aimed at reducing indoor exposures in inner-city homes to refine current recommendations regarding environmental control practices.

References


