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Rationale: Although cigarette smoking is the most important cause of chronic obstructive pulmonary disease (COPD), a substantial proportion of COPD cases cannot be explained by smoking alone.

Objectives: To evaluate the risk factors for COPD besides personal cigarette smoking.

Methods: We constituted an ad hoc subcommittee of the American Thoracic Society Environmental and Occupational Health Assembly. An international group of members was invited, based on their scientific expertise in a specific risk factor for COPD. For each risk factor area, the committee reviewed the literature, summarized the evidence, and developed conclusions about the likelihood of it causing COPD. All conclusions were based on unanimous consensus.

Measurements and Main Results: The population-attributable fraction for smoking as a cause of COPD ranged from 9.7 to 97.9%, but was less than 80% in most studies, indicating a substantial burden of disease attributable to non-smoking risk factors. On the basis of our review, we concluded that specific genetic syndromes and occupational exposures were causally related to the development of COPD. Traffic and other outdoor pollution, secondhand smoke, biomass smoke, and dietary factors are associated with COPD, but sufficient criteria for causation were not met. Chronic asthma and tuberculosis are associated with irreversible loss of lung function, but there remains uncertainty about whether there are important phenotypic differences compared with COPD as it is typically encountered in clinical settings.

Conclusions: In public health terms, a substantive burden of COPD is attributable to risk factors other than smoking. To prevent COPD-related disability and mortality, efforts must focus on prevention and cessation of exposure to smoking and these other, less well-recognized risk factors.

Keywords: pulmonary disease, chronic obstructive; pulmonary emphysema; chronic bronchitis; respiratory function tests; genetics; diet; asthma; air pollution; air pollution, indoor; tobacco smoke pollution; biomass; occupational exposure; occupational diseases; diet; nutritional status; tuberculosis

EXECUTIVE SUMMARY

Cigarette smoking is the most important single causal factor for developing chronic obstructive pulmonary disease (COPD). The view that cigarette smoking is the sole meaningful factor in the epidemiology and natural history of COPD, however, is a misconception. Our review indicates that a substantial proportion of COPD cases cannot be explained by smoking, especially among younger persons, females, and residents of developing countries. We reviewed the literature to evaluate the impact of novel, less traditional risk factors for COPD. Strong evidence implicates several rare genetic syndromes (such as α1-antitrypsin deficiency) and occupational exposures as causes of COPD. Traffic and other outdoor pollution, secondhand smoke, biomass smoke, and dietary factors are likely causes of COPD, although the evidence is not sufficient to infer a causal relationship for these risk factors. Chronic asthma and tuberculosis are likely causes of lung function decrement and irreversible airway obstruction. It remains uncertain, however, whether the clinical features and natural history of these diseases, when accompanied by irreversible airway obstruction, are the same as COPD as it is typically encountered in clinical settings. In research terms, further prospective studies with adequate numbers of nonsmokers and rigorous control for confounding variables are needed to establish the causal effects of outdoor pollution, secondhand smoke, biomass smoke, dietary factors, chronic asthma, and tuberculosis on COPD causation. In public health terms, a substantive burden of COPD is attributable to risk factors other than smoking. To prevent COPD-related disability and mortality, efforts must focus on prevention and cessation of exposure to smoking and these other, less well-recognized risk factors.
INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a common disease, affecting 5–10% of the U.S. population (1, 2). During the past two decades, death from COPD has continued to increase, especially among women (1, 2). Disability from the disease is substantial, and is expected to increase in the United States and worldwide (3). Despite these trends, efforts to treat COPD have been disappointing. The only medical therapies that clearly reduce disease progression and mortality are smoking cessation and supplemental oxygen (4, 5). Because currently available treatments have minimal impact on disease progression, a strategy to prevent the development of COPD is a critical priority.

Personal direct cigarette smoking is the most important single causal factor for developing COPD. The view that cigarette smoking is the sole meaningful factor in the epidemiology and natural history of COPD, however, is a misconception. Although direct cigarette smoking is the major cause of COPD, a substantial minority of cases cannot be attributed solely to this risk factor. Other exposures may be important in the genesis of the disease.

The development of successful preventive strategies requires better elucidation of the untraditional risk factors for COPD besides smoking. In addition, it is likely that other risk factors biologically interact with cigarette smoking and potentiate the development of airflow obstruction. Consequently, there is an urgent need to evaluate the contribution of novel risk factors for COPD at the population level, both in the United States and worldwide. In this statement, we elucidate the contribution of untraditional risk factors for COPD: genetic factors, longstanding asthma, outdoor air pollution, secondhand smoke exposure, biomass smoke and indoor air pollution, occupational exposures, diet, and tuberculosis.

METHODS

Committee Process

Committee members were invited on the basis of their scientific expertise in a specific risk factor for COPD. Because of the global focus of the document, an international group of members was recruited. Each member independently searched the literature (see below), assessed the individual articles, prepared a written summary of the risk factor area that evaluated the sum of evidence, developed preliminary recommendations about possible causation, and presented the findings and preliminary recommendations to the entire committee. Consensus on the conclusions was reached among members of the committee by discussion and vote (there were two in-person meetings and three teleconferences). All conclusions were based on unanimous consensus. All members reviewed and approved the entire final draft by e-mail.

Literature Search

For each risk factor, the published medical literature was rigorously reviewed, using the National Library of Medicine MEDLINE database until May 1, 2008 (see Appendix E1 in the online supplement). Snowball searching was employed, based on reference lists of identified publications and electronic citations. Published peer-reviewed English language papers were included. Studies were included if they had acceptable methodological rigor, included a substantial number of lifelong “never” smokers (i.e., at least 20% of the overall sample or 100 subjects), employed sufficient statistical control for personal cigarette smoking in stratified or multivariable analysis, used valid exposure measurement methodology for the risk factor under consideration, and included one of the definitions of COPD detailed below. Although the literature review was thorough, no systematic assessment of publication bias was performed.

The definition of COPD posed a challenge for this review. Epidemiologic studies differ from clinical practice because they often study large populations that reside in broad geographical areas and employ survey-based methodology. Consequently, a substantive proportion of epidemiologic studies do not include spirometry because of study-specific logistical constraints. Moreover, the measurement of COPD has changed over time, shifting from a paradigm of chronic bronchitis and emphysema to that of objectively measured irreversible airflow obstruction.

The committee adopted a broad and inclusive approach to considering studies of risk factors for COPD. Studies were included if they used any of the following definitions: Global Initiative for Chronic Obstructive Lung Disease (GOLD) definition (FEV$_1$/FVC < 0.70) or other spirometry-based definition of airway obstruction (e.g., British Thoracic Society definition), chronic bronchitis (i.e., cough and sputum production for at least 3 mo/yr for at least 2 yr), or a self-reported diagnosis of chronic bronchitis, emphysema, or COPD. Studies of bronchiectasis or cystic fibrosis were not included.

In our assessment of the evidence, we used a hierarchical weighting system that took into account the specificity of the COPD definition used in each study. For example, the GOLD definition of COPD (which uses the same spirometric cutoffs as the American Thoracic Society/European Respiratory Society guidelines) was considered to be the highest standard of evidence, whereas self-reported or physician-diagnosed chronic bronchitis, emphysema, or COPD were considered less specific for COPD. The highest categories of evidence (“evidence is sufficient to infer a causal relationship” or “sufficient evidence of an association”) required studies that used a spirometric definition of COPD. Otherwise, the highest level of evidence that could be achieved was “limited/suggestive evidence of an association.”

Studies that evaluated respiratory symptoms only, without using the formal epidemiologic definition of chronic bronchitis, were considered to be supportive studies only and were not systematically reviewed. Similarly, studies that evaluated the impact of exposure on the clinical course of established COPD were not systematically reviewed.

The committee recognizes that COPD is a heterogeneous condition that has a single common denominator: chronic airflow obstruction. The current state-of-the-art does not allow separation of the disease into subphenotypes. As clinical science advances, the impact of specific risk factors, besides smoking, on the risk of COPD phenotypes can be studied. At present, we adopted an approach that used the available epidemiology to evaluate the contribution of nonsmoking risk factors for COPD. This clinical heterogeneity of COPD definitions likely introduced nondifferential misclassification, which reduced the precision of effect estimates and introduced a conservative bias (i.e., toward the null).

Two risk factor areas, asthma and tuberculosis, warrant special comment. Because they can cause irreversible airflow obstruction, we have included them in this review with appropriate caveats in each section.

Evidence Synthesis and Evaluation

Evidence was analyzed to classify the association between each risk factor and COPD, using the criteria enumerated by Sir Austin Bradford Hill, which were used by the U.S. Surgeon General beginning in 1964 and later modified for diseases that have multiple causative exposures such as COPD (i.e., “mod-
SMOKING AND POPULATION-ATTRIBUTABLE RISK FOR COPD

The strength of evidence that smoking is a cause of COPD has been growing for more than 40 years and has been extensively reviewed in three U.S. Surgeon General’s Reports (9–11). The 1984 Surgeon General Report concluded that 80–90% of COPD in the United States is attributable to smoking. In our review of studies, the estimated fraction of COPD mortality attributable to smoking was 54% for men 30–69 years of age and 52% for men 70 years of age or older (12). The corresponding attributable fractions for women were 24 and 19%, respectively. The attributable fractions were higher in industrialized countries (84 and 77% for men, and 62 and 61% for women) compared with developing countries (49 and 45% for men, and 20 and 12% for women). The purpose of this section is to summarize evidence on the magnitude of the population-attributable fraction (PAF) and sources of variation in the estimates for smoking as a cause of COPD (see Appendix E2 for calculation of PAF).

Of the relevant studies (2000–2008), most have been conducted in European and Asian countries (Table 1 and Tables E1–E3; see Appendix E4 in the online supplement for tables with the prefix “E”). These studies have consistently demonstrated an association between smoking and COPD in cross-sectional and cohort studies using different definitions of COPD that included spirometric criteria, self-reported diagnosis, and death certificates. Moreover, there is a consistent exposure–response relationship and the cohort studies support the causal criterion of temporality (i.e., the exposure precedes the onset of disease).

Although this evidence confirms that the majority of COPD is attributable to smoking, there is wide variation in the estimated PAFs from these studies, ranging from 9.7 to 97.9% (Table 1 and Tables E1–E3) (12–35). A number of factors may contribute to this variation including differences between studies in age and sex distribution, prevalence of current and former smokers, diagnostic misclassification, method to calculate PAF, and exposure to other concurrent risk factors. Studies evaluating the PAF for COPD mortality are also affected by regional differences in death certificate coding. In general, the population-attributable fractions have been lower among younger populations (14, 26), females (20), current smokers (16, 27), and developing countries (12, 29). The lower PAF among younger or female populations likely reflects a greater proportion of COPD attributable to risk factors besides smoking that are discussed in this statement, such as occupational exposures or biomass smoke.

The majority of PAF estimates are less than 80%, indicating that other risk factors, besides cigarette smoking, are important in the development of COPD. Further evidence of the role of other risk factors is the occurrence of COPD among never-smokers, with prevalence estimates ranging from approximately 3 to 15% in various populations using different methods (31, 36). In addition, some of these less traditional risk factors may contribute to the development of COPD in some populations. However, the exact contribution of these factors is not clear and requires further research.

Implications for COPD

Normal lung development is characterized by growth of pulmonary function during childhood and adolescence until peak lung function, as measured by forced expiratory volume in 1 second (FEV<sub>1</sub>), is reached by age 18–20 years. Pulmonary function then plateaus and then declines as a feature of normal aging. In theory, exposures that affect the growth phase (leading to decreased peak FEV<sub>1</sub>), plateau phase (leading to shortened plateau period), or subsequent decline in pulmonary function (accelerated decline) could lead to COPD (Figure 1). Consequently, studies that found an association between an exposure of interest (e.g., outdoor air pollution) and lower FEV<sub>1</sub> have relevance for COPD causation, even if these studies did not evaluate COPD as a specific study outcome.
interact with smoking to further increase the risk of COPD. Each risk factor area is reviewed below.

**NONSMOking RISK FACTORS FOR COPD**

**Genetic Factors and the Risk of COPD**

Although cigarette smoking is the major risk factor for COPD, there is strong evidence that genetic factors influence the development of COPD in response to smoking (37). The role of genetic factors in nonsmokers with COPD has been less widely studied, but several lines of evidence suggest that genetic factors are at least as important in the development of COPD among nonsmokers as they are among smokers.

**Familial studies of pulmonary function in nonsmokers.** Both twin and family studies have been performed to assess the potential impact of genetic factors on pulmonary function (Table 2). In twin studies, higher concordance among monozygotic (MZ) than dizygotic (DZ) twins was suggestive of genetic influences on the condition. In a small study of nonsmoking twins, genetic factors appeared to influence lung volumes and maximal expiratory flow curves (38). However, a larger study of nonsmoking twins did not find conclusive evidence of genetic influences on pulmonary function (39). Several other twin studies found significant heritability for FEV1, but many smokers were included in those studies (40, 41).

Familial aggregation of a condition is a necessary, but not sufficient, prerequisite for genetic factors to influence a complex trait such as COPD. In addition to genetic factors, a common familial environment can also cause familial aggregation; therefore, statistical methods are used to estimate the genetic contribution. Various family studies (Table 2) have assessed familial aggregation of pulmonary function. However, only a few of these studies have focused exclusively on nonsmokers or performed stratified analyses of nonsmokers. Most studies, which have included both smokers and nonsmokers, found evidence of significant familial correlations or heritability for FEV1. In one of the few studies of nonsmokers exclusively, there was evidence of significant familial aggregation of both FEV1 and FVC, which could have been caused by genetic factors or common familial environment (42).

In studies focusing on families of identified COPD case subjects, first-degree relatives of COPD case subjects who currently or previously smoked had a higher risk of airflow obstruction compared with control subjects. There was, however, no increased risk of airflow obstruction among nonsmoking first-degree relatives (43, 44). In a larger sample from the Boston Early-onset COPD Study, nonsmoking first-degree relatives of early-onset COPD case subjects had lower values for flows at mid-lung volumes (forced expiratory flow, mid-expiratory phase [FEF25–75] and FEF25–75/FVC) compared with nonsmoking control subjects (45).

Overall, twin and familial aggregation studies suggest that genetic factors likely influence variation in pulmonary function in nonsmokers, but these results do not necessarily indicate that genetic factors increase the risk of developing a clinical diagnosis of COPD.

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**TABLE 1. COHORT STUDIES OF RISK OF SMOKING FOR SPIROMETRY-DEFINED CHRONIC OBSTRICTIVE PULMONARY DISEASE**

<table>
<thead>
<tr>
<th>Study (Ref.)</th>
<th>Follow-up Period</th>
<th>Population</th>
<th>Sample Size</th>
<th>Smoking Status</th>
<th>Outcome Measurement</th>
<th>Adjusted OR (95% CI)</th>
<th>Population-attributable Fraction (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lindberg et al., 2005; Sweden (35)</td>
<td>Cohort, 10-yr follow-up</td>
<td>Population-based sample, 46–77 yr</td>
<td>1,109</td>
<td>Persistent smokers, 24.1%</td>
<td>FEV1/FVC &lt;0.7</td>
<td>BTS Persistent smokers, 5.37 (2.82–10.26)</td>
<td>BTS: 48.3 GOLD: 48.6</td>
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<tr>
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<td></td>
<td>Persistent ex-smokers, 26.3%</td>
<td>FEV1/FVC &lt;0.7</td>
<td>Persistent ex-smokers, 1.01 (0.46–2.17)</td>
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<td></td>
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<td></td>
<td></td>
<td>Quitters, 12.0%</td>
<td>FEV1/FVC &lt;0.7</td>
<td>Quitters, 2.32 (1.02–5.3)</td>
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<td></td>
<td>Restarters, 2.0%</td>
<td>FEV1/FVC &lt;0.7</td>
<td>Restarters, 3.13 (0.65–15.9)</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Nonsmokers, 34.1%</td>
<td>FEV1/FVC &lt;0.7</td>
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<tr>
<td>Lindberg et al., 2006; Sweden (19)</td>
<td>Cohort, 7-yr follow-up</td>
<td>Population-based sample, 46–77 yr</td>
<td>963</td>
<td>Smokers, 24%</td>
<td>FEV1/FVC &lt;0.7</td>
<td>Ex-smokers, 4.01 (1.52–10.55)</td>
<td>76.2</td>
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<td></td>
<td>Ex-smokers, 35%</td>
<td>FEV1/FVC &lt;0.7</td>
<td>Smokers, 9.92 (3.82–25.82)</td>
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<td></td>
<td>Nonsmokers, 41%</td>
<td>FEV1/FVC &lt;0.7</td>
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<tr>
<td>Lokke et al., 2006; Denmark (21)</td>
<td>Cohort, 25-yr follow-up</td>
<td>Population-based sample</td>
<td>8,045</td>
<td>Continuous smokers, 30.4%</td>
<td>FEV1/FVC &lt;70%</td>
<td>Continuous smokers, 6.3 (4.2–9.5)</td>
<td>74.6</td>
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<td></td>
<td>Ex-smokers, 18.3%</td>
<td>FEV1/FVC &lt;80%</td>
<td>Ex-smokers, 1.1</td>
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<td></td>
<td>Early cessation, 4.6%</td>
<td>FEV1/FVC &lt;80%</td>
<td>Early cessation, 1.8</td>
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<td></td>
<td>Intermediate cessation, 7.6%</td>
<td>FEV1/FVC &lt;80%</td>
<td>Intermediate cessation, 2.8</td>
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<td></td>
<td></td>
<td>Late cessation, 10.4%</td>
<td>FEV1/FVC &lt;80%</td>
<td>Late cessation, 4.7</td>
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<td></td>
<td></td>
<td>Nonsmokers, 28.7%</td>
<td>FEV1/FVC &lt;70%</td>
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<tr>
<td>de Marco et al., 2007; Europe (14)</td>
<td>Cohort; median follow-up, 8.9 yr</td>
<td>Random population sample</td>
<td>5,002</td>
<td>Ever-smokers (&lt;15 pack-years), 37.6%</td>
<td>FEV1/FVC &lt;70%</td>
<td>Ever-smokers (&lt;5 pack-years), 1.42 (1.02–1.98)</td>
<td>39.6</td>
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<td></td>
<td>Ever-smokers (&gt;15 pack-years), 18.0%</td>
<td>FEV1/FVC &lt;70%</td>
<td>Ever-smokers (&gt;15 pack-years), 3.76 (2.76–5.12)</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Nonsmokers, 44.4%</td>
<td>FEV1/FVC &lt;70%</td>
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</tr>
</tbody>
</table>

*Definition of abbreviations: BTS = British Thoracic Society; CI = confidence interval; GOLD = Global Initiative for Chronic Obstructive Long Disease; OR = odds ratio.*
<table>
<thead>
<tr>
<th>Study (Ref.)</th>
<th>Type of Study</th>
<th>Population</th>
<th>Sample Size</th>
<th>Respiratory Outcome Measurement</th>
<th>Findings*</th>
<th>Study Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Man, 1976 (38)</td>
<td>Twin</td>
<td>Asymptomatic nonsmoking same-sex twin pairs between ages 18 and 48 yr</td>
<td>10 pairs of monozygotic twins and 6 pairs of dizygotic twins</td>
<td>Lung volumes and maximal expiratory flow-volume curves</td>
<td>Smaller intrapair differences for MZ than DZ twins for vital capacity and maximal flow rate at 60% of TLC</td>
<td>Small sample size No adjustment for height</td>
</tr>
<tr>
<td>Hubert, 1982 (40)</td>
<td>Twin</td>
<td>Middle-aged males from NHLBI Twin Study</td>
<td>127 pairs of monozygotic twins and 141 pairs of dizygotic twins; only 148 subjects were nonsmokers</td>
<td>FEV1 and FVC</td>
<td>Significant heritability for FEV1 (0.74) after adjustment for age, height, weight, and pack-years. Significant heritability for FVC not shown</td>
<td>Most study participants were smokers</td>
</tr>
<tr>
<td>Redline, 1987 (41)</td>
<td>Twin</td>
<td>Same-sex adult twins in the Greater Boston Twin Registry</td>
<td>256 monozygotic and 158 dizygotic twin pairs; only 163 individuals were nonsmokers</td>
<td>FEV1 and FVC</td>
<td>Significant intrapair correlations for both FEV1 and FVC among MZ twins, with magnitude of correlations approximately twice as great in MZ vs. DZ pairs</td>
<td>Most study participants were smokers</td>
</tr>
<tr>
<td>Ghio, 1989 (39)</td>
<td>Twin</td>
<td>Same-sex twin pairs who were asymptomatic university students and nonsmokers</td>
<td>74 pairs of asymptomatic, nonsmoking twins (47 MZ, 27 DZ)</td>
<td>FEV1, FVC, FEF25–75, lung volumes, and DLCO</td>
<td>No conclusive evidence of significant heritability of any phenotype studied after height adjustment, although FEF25–75 was borderline</td>
<td>Small sample size Young age of subjects (mean, 20 yr)</td>
</tr>
<tr>
<td>Higgins, 1975 (288)</td>
<td>Family</td>
<td>Residents of Tecumseh, MI</td>
<td>9,226 subjects, general population</td>
<td>FEV1</td>
<td>Significant correlations between FEV1 of parents and children under age 40 yr. Significant correlations for FEV1 values of same-sex siblings at all ages</td>
<td>Smokers were included, but no adjustment for smoking. No separate analysis of nonsmokers</td>
</tr>
<tr>
<td>Tager, 1976 (289)</td>
<td>Family</td>
<td>Households from East Boston, MA</td>
<td>469 individuals from 148 households</td>
<td>FEV1</td>
<td>Significant correlations between mid-parental FEV1 and child’s FEV1. Significant correlations between siblings’ FEV1. No significant correlations between spouses’ FEV1</td>
<td>Smokers were included, but no adjustment for smoking. No separate analysis of nonsmokers</td>
</tr>
<tr>
<td>Lewitter, 1984 (290)</td>
<td>Family</td>
<td>Families from East Boston, MA</td>
<td>1,358 individuals from 404 nuclear families</td>
<td>FEV1 and FEF25–75</td>
<td>Path analysis demonstrated: Significant heritability for FEV1 (0.45) Significant heritability for FEF25–75 (0.45)</td>
<td>Smokers were included, with adjustment for smoking status. No separate analysis of nonsmokers</td>
</tr>
<tr>
<td>Devor, 1984 (42)</td>
<td>Family</td>
<td>Mennonite families in Kansas</td>
<td>307 asymptomatic nonsmokers in nuclear families</td>
<td>FEV1 and FVC</td>
<td>Path analysis using the XTAU model demonstrated: Significant transmissible variation for both FEV1 (0.17) and FVC (0.20). Significant effects of shared sibling environment on sibling correlations</td>
<td>Unable to separate cultural from genetic influences</td>
</tr>
<tr>
<td>Lebowitz, 1984 (291)</td>
<td>Family</td>
<td>Nuclear families from the Tucson Epidemiology Study of Airway Obstructive Diseases</td>
<td>899 individuals in nuclear families</td>
<td>FEV1, FVC, Vmax50, and Vmax75</td>
<td>Significant correlations for parent-child FEV1 and FVC without covariate adjustment. After adjustment for ponderal index, no significant familial correlations were noted</td>
<td>Offspring were largely adolescent, so impact of growth may have been magnified. Smokers were included, with adjustment for smoking status. No separate analysis of nonsmokers</td>
</tr>
<tr>
<td>Astemborski, 1985 (292)</td>
<td>Family</td>
<td>Families ascertained through control subjects in Baltimore</td>
<td>439 adults from 108 nuclear families</td>
<td>FEV1 and FEV1/FVC</td>
<td>Variance component analysis demonstrated: Additive genetic factors accounted for 28% of variation in FEV1. Additive genetic factors accounted for 24% of variation in FEV1/FVC</td>
<td>Smokers were included, with adjustment for smoking status. No separate analysis of nonsmokers</td>
</tr>
</tbody>
</table>
Development of airflow obstruction among PI Z subjects (54).

Dusts (52, 53). Genetic modifiers also likely influence the variable wheezing, and occupational exposure to respiratory irritants or dusty, and respiratory irritants or dusts (52, 53).

A Danish study found that PI Z nonsmoking subjects had similar airflow obstruction and respiratory symptoms has been observed (50).

Moreover, family-based genetic association studies of COPD have limited enrollment to current or ex-smokers, because of the likely gene-by-smoking interactions involved in COPD susceptibility (66). Family-based association analyses have included, with adjustment for smoking status No separate analysis of nonsmokers.

Vital capacity; Vmax75

Maximal expiratory flow rate at 75% of vital capacity. DZ = dizygotic twins; FEF25–75 = forced expiratory flow, mid-expiratory phase; MZ = monozygotic twins; Vmax50 = maximal expiratory flow rate at 50% of vital capacity; Vmax50 = maximal expiratory flow rate at 75% of vital capacity.

Many of these studies provide estimates of heritability, a measurement in genetic epidemiology that estimates the fraction of total phenotypic variation that is due to genetic factors.

TABLE 2. (CONTINUED)

<table>
<thead>
<tr>
<th>Study (Ref.)</th>
<th>Type of Study</th>
<th>Population</th>
<th>Sample Size</th>
<th>Respiratory Outcome</th>
<th>Findings*</th>
<th>Study Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Silverman, 1998 (43)</td>
<td>Family</td>
<td>Extended pedigrees of severe early-onset COPD probands and control probands</td>
<td>204 first-degree relatives of COPD probands and 83 control family members</td>
<td>FEV1, FEV1/FVC, FEV1&lt;80% pred, and FEV1&lt;60% pred</td>
<td>Reduced FEV1 and FEV1/FVC and increased risk of FEV1 &lt; 60% and FEV1&lt;80% found in smoking first-degree relatives of subjects with COPD compared with smoking control subjects. No increased risk for reduced FEV1 or FEV1/FVC in nonsmoking relatives of COPD probands compared with nonsmoking control subjects.</td>
<td>Small sample size for control subjects</td>
</tr>
<tr>
<td>Palmer, 2001 (293)</td>
<td>Family</td>
<td>Nuclear families from Busselton in Western Australia</td>
<td>1,874 individuals from 468 nuclear families, using spirometry when subject was an adult</td>
<td>FEV1 and FVC</td>
<td>Heritability estimates of 0.39 for FEV1 and 0.41 for FVC</td>
<td>Smokers were included, with adjustment for smoking status. No separate analysis of nonsmokers.</td>
</tr>
<tr>
<td>McCloskey, 2001 (44)</td>
<td>Family</td>
<td>Nuclear families of COPD case subjects in the UK</td>
<td>173 siblings of COPD case subjects and 419 population-based control subjects</td>
<td>FEV1 and FEV1/FVC</td>
<td>Current or ex-smoking siblings of COPD probands had odds ratio of 4.7 for COPD (FEV1 &lt;80% pred and FEV1/FVC &lt; 0.7) compared with control smokers. All of the nonsmoking sibling of COPD probands had normal spirometry.</td>
<td>Small sample of nonsmoking siblings.</td>
</tr>
<tr>
<td>DeMeo, 2004 (45)</td>
<td>Family</td>
<td>Extended pedigrees of severe, early-onset COPD probands and control probands</td>
<td>333 first-degree relatives of COPD probands and 83 control family members</td>
<td>FEF25–75 and FEF25–75/FVC</td>
<td>Significantly lower FEF25–75 and FEF25–75/FVC in smoking first-degree relatives of COPD probands compared with smoking control subjects. Significantly lower FEF25–75 and FEF25–75/FVC in nonsmoking relatives of COPD probands compared with nonsmoking control subjects.</td>
<td>Small sample size for control subjects.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study (Ref.)</th>
<th>Type of Study</th>
<th>Population</th>
<th>Sample Size</th>
<th>Respiratory Outcome</th>
<th>Findings*</th>
<th>Study Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Silverman, 1998 (43)</td>
<td>Family</td>
<td>Extended pedigrees of severe early-onset COPD probands and control probands</td>
<td>204 first-degree relatives of COPD probands and 83 control family members</td>
<td>FEV1, FEV1/FVC, FEV1&lt;80% pred, and FEV1&lt;60% pred</td>
<td>Reduced FEV1 and FEV1/FVC and increased risk of FEV1 &lt; 60% and FEV1&lt;80% found in smoking first-degree relatives of subjects with COPD compared with smoking control subjects. No increased risk for reduced FEV1 or FEV1/FVC in nonsmoking relatives of COPD probands compared with nonsmoking control subjects.</td>
<td>Small sample size for control subjects</td>
</tr>
<tr>
<td>Palmer, 2001 (293)</td>
<td>Family</td>
<td>Nuclear families from Busselton in Western Australia</td>
<td>1,874 individuals from 468 nuclear families, using spirometry when subject was an adult</td>
<td>FEV1 and FVC</td>
<td>Heritability estimates of 0.39 for FEV1 and 0.41 for FVC</td>
<td>Smokers were included, with adjustment for smoking status. No separate analysis of nonsmokers.</td>
</tr>
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<td>McCloskey, 2001 (44)</td>
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<td>Small sample size for control subjects.</td>
</tr>
</tbody>
</table>

**Definition of abbreviations:** % pred = percentage of predicted value; COPD = chronic obstructive pulmonary disease; DLCO = diffusing capacity of the lung for carbon monoxide; DZ = dizygotic twins; FEF25–75 = forced expiratory flow, mid-expiratory phase; MZ = monozygotic twins; Vmax50 = maximal expiratory flow rate at 50% of vital capacity; Vmax50 = maximal expiratory flow rate at 75% of vital capacity.

* Many of these studies provide estimates of heritability, a measurement in genetic epidemiology that estimates the fraction of total phenotypic variation that is due to genetic factors.

Genetic linkage studies have not been widely performed in families of nonsmokers. A linkage study of 1,183 individuals from 200 Dutch families evaluated nonsmokers in a stratified analysis (46). It found suggestive evidence of linkage of prebronchodilator FEV1/VC on chromosome 14; they also found several other genomic regions with possible linkage to phenotypes defined by spirometry.

**Severe α1-antitrypsin deficiency in nonsmokers.** Severe α1-antitrypsin (AAT) deficiency is a well-established genetic risk factor for COPD in nonsmokers. Case series of protease inhibitor (PI) Z subjects (i.e., homozygous for the AAT Z allele) have clearly demonstrated that cigarette smoking leads to a markedly increased risk of COPD and reduced survival; nonsmoking PI Z subjects are also at increased risk for developing COPD, although to a lesser degree (47–49). Among nonsmoking PI Z subjects, marked variability in the development of airflow obstruction and respiratory symptoms has been observed (50). A Danish study found that PI Z nonsmoking subjects had similar overall survival to the general Danish population (51). Moreover, specific risk factors appear to increase the risk of lower pulmonary function, including older age (greater than 50 yr), male sex, wheezing, and occupational exposure to respiratory irritants or dusts (52, 53). Genetic modifiers also likely influence the variable development of airflow obstruction among PI Z subjects (54).

**Other rare genetic syndromes in nonsmokers.** In addition to AAT deficiency, various other rare genetic syndromes have been suggested as possible causes of COPD in nonsmokers. Cutis laxa is a rare inherited disorder of the elastic fibers, which in some cases is caused by mutations in the elastin gene (55). Cutis laxa has been clearly demonstrated to cause emphysema in childhood and adolescence in some subjects, even if they are nonsmokers (56, 57). Marfan syndrome (58, 59) and Ehlers-Danlos syndrome (60) have been associated with lung blebs and pneumothorax, but there is no definitive relationship with COPD. Similarly, Birt-Hogg-Dubé syndrome (61, 62) and familial spontaneous pneumothorax syndrome (63), which are both caused by mutations in the folliculin gene (64, 65), can cause lung blebs and pneumothorax in nonsmokers, but they have not been clearly associated with COPD.

**Genetic association studies in nonsmokers.** Most case–control genetic association studies of COPD have limited enrollment to current or ex-smokers, because of the likely gene-by-smoking interactions involved in COPD susceptibility (66). Family-based association analyses have included, with adjustment for smoking status No separate analysis of nonsmokers. A study using data from the Framingham Heart Study focused on a positional candidate gene, SMOC2, located within a region of linkage to FEV1 on chromosome 6.
TABLE 3. CROSS-SECTIONAL STUDIES DEMONSTRATING IRREVERSIBLE AIRWAY OBSTRUCTION IN CLINICAL SAMPLES OF ADULTS WITH ASTHMA

<table>
<thead>
<tr>
<th>Study (Ref.)</th>
<th>Population</th>
<th>Proportion of Smokers</th>
<th>Prednisone Reversal</th>
<th>Lung Function Outcome Measurement</th>
<th>Outcome</th>
<th>Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brown, 1984 (69)</td>
<td>89 consecutive patients</td>
<td>43%</td>
<td>Yes</td>
<td>FEV1 &lt;70% predicted</td>
<td>19%</td>
<td>Age, duration, severity</td>
</tr>
<tr>
<td>ten Brinke, 2001 (75)</td>
<td>136 patients with severe disease</td>
<td>30% (&lt;10 pack-years)</td>
<td>No*</td>
<td>FEV1/FVC &lt; 75% predicted</td>
<td>49%</td>
<td>Age, duration, sputum eosinophils</td>
</tr>
<tr>
<td>Ulrik, 1999 (70)</td>
<td>92 patients</td>
<td>None</td>
<td>No</td>
<td>FEV1 &lt;80% predicted</td>
<td>23%</td>
<td>Large initial dilator response</td>
</tr>
<tr>
<td>Vonk, 2003 (76)</td>
<td>228 patients with asthma</td>
<td>30% patients</td>
<td>No</td>
<td>Irreversibility</td>
<td>16%</td>
<td>Severity: low initial FEV1, reactivity, reversibility</td>
</tr>
<tr>
<td>Cassino, 2000 (71)</td>
<td>75 patients &gt;60 yr</td>
<td>None</td>
<td>No</td>
<td>Mean FEV1 (% predicted)</td>
<td>Long duration = 60% vs. short duration = 80%</td>
<td>Duration, not severity</td>
</tr>
<tr>
<td>Bumbacea, 2004 (74)</td>
<td>66 patients with severe disease</td>
<td>30%</td>
<td>No*</td>
<td>Mean FEV1 (% predicted); compare reversible with irreversible</td>
<td>Nonreversible = 50% vs. reversible = 80% predicted</td>
<td>Age, duration Blood eosinophils Bronchial disease on HRCT</td>
</tr>
<tr>
<td>Hudon, 1997 (77)</td>
<td>36 patients (18 reversible, 18 nonreversible), age and sex matched</td>
<td>14% (&lt;7 pack-years)</td>
<td>Yes</td>
<td>Mean FEV1 (% predicted); compare reversible with irreversible</td>
<td>Nonreversible = 49% vs. reversible = 80%</td>
<td>Duration Bronchial disease on HRCT</td>
</tr>
</tbody>
</table>

* Clinical improvement after treatment with prednisone.

(68). In nonsmokers, these investigators found significant associations between several single-nucleotide polymorphisms in SMO2 with FEV1 and FVC.

Genetic risk factors for COPD: conclusions. There is limited/suggestive evidence of familial aggregation of pulmonary function among nonsmokers. α1-Antitrypsin deficiency and cutis laxa are clearly risk factors for COPD in nonsmokers with sufficient evidence to infer a causal relationship. Other genetic determinants of COPD likely exist; however, large-scale genetic studies have not been performed to identify these specific genetic determinants of COPD in nonsmokers.

Long-standing Asthma and the Risk of COPD

Chronic airway obstruction in adults with asthma. Chronic airway obstruction is defined as persistence of airway obstruction (i.e., abnormally low FEV1) in spite of pharmacological attempts at reversal. The presence of such irreversible obstruction among patients with asthma, including nonsmokers, was first clearly identified by Brown, Greville, and Finucane, who studied a clinic-based population (69) (Table 3). Subsequent case series revealed a substantive proportion of patients with asthma with irreversible airway obstruction (70–77). Most studies indicated that the irreversible obstruction occurred in older patients with a longer duration of asthma; duration of asthma appears to be more important than chronological age (71, 72). Development of asthma in later adulthood (>65 yr) was associated with less airway obstruction than among those with early-onset asthma, further suggesting an effect of asthma duration on chronic airway obstruction (73). Therefore, the evidence suggests that a longer duration of asthma may lead to more severe airway obstruction.

Adults with asthma may develop radiographic features suggestive of COPD. Thoracic computed tomography (CT) scans revealed bronchial wall thickening among patients with asthma with irreversible airway obstruction (74, 77–80). In addition, CT scans revealed evidence of emphysema in some nonsmoking patients with asthma, especially those with irreversible airway obstruction, longer duration of disease, and greater asthma severity (78–83).

Rate of lung function decline in adults with asthma. Beginning at about age 25 years, an annual decline in FEV1 (20 ml/yr) is a normal feature in healthy nonsmoking subjects (84, 85). Several studies revealed an excess decline in FEV1 of approximately 20 ml/year in subjects with asthma compared with subjects without asthma (Table E4) (84, 86–96). This decline is greater in smoking subjects with asthma, but also occurs among nonsmoking adults with asthma (84, 87, 89, 90, 95, 96). Analysis of data from the Copenhagen City Heart Study indicated that asthma was associated with an accelerated decline in pulmonary function in both smokers and nonsmokers during 15 years of follow-up (overall mean FEV1 decline of 38 ml/yr in asthma vs. 22 ml/yr in those without asthma) (84, 90).

Other factors associated with an excess decline in FEV1 among persons with asthma appear to be as follows: low baseline lung function (FEV1 % predicted) (87, 92, 95), less reversibility to β2-agonists (70, 92, 93), more severe bronchial hyperresponsiveness (87, 97–100), mucus production (84, 101), male sex (90), and frequent exacerbations (102). The association between atopic status and longitudinal changes in lung function is not clear, with studies showing no effect (87, 103), a positive effect (99), and a negative effect of atopy on lung function decline (92, 104).

Childhood asthma. Although there have been few cohort studies monitoring children with asthma into adulthood, a history of childhood asthma appears to predispose to lower FEV1 in adulthood (104–106). There is evidence of an exposure–response gradient, with greater childhood asthma severity relating to poorer adult FEV1. In the Tucson study, persistent wheezing between ages 3 and 6 years, which is associated with an asthmatic phenotype, was associated with lower FEV1 during early adulthood (age, 16 yr) (107). Taken together, the evidence suggests that childhood asthma leads to lung function impairment that persists into adulthood.

Among individuals with asthma, childhood factors associated with a low FEV1 in adulthood are as follows: low baseline FEV1...
Air pollution and COPD: conclusions. There is sufficient evidence of an association between chronic asthma and both chronic airway obstruction and accelerated loss of pulmonary function. Because airway obstruction can lead directly to COPD, it is likely that asthma, with or without additional risk factors, can predispose a person to develop COPD. Studies demonstrating radiographic evidence of emphysema among life-long nonsmokers with asthma also support the possible role of chronic asthma in the genesis of COPD. It remains uncertain, however, whether adults with asthma who meet spirometric criteria for COPD, such as the GOLD criteria, are phenotypically and pathologically similar to or distinct from “typical” COPD as it is usually encountered in clinical practice. One study showed that adults with asthma and fixed airway obstruction differ from those with COPD in radiographic appearance (lower HRCT emphysema scores) and airway inflammation (more eosinophils and fewer neutrophils) (116), although other investigators have found airway neutrophilia in severe asthma that is more similar to COPD (117, 118). Further research will be necessary to define subphenotypes of COPD and the relationship to chronic asthma and airway remodeling.

Outdoor Air Pollution (from Traffic and Other Sources)

Outdoor air pollution is a mixture of hundreds of pollutants that originate from industry, traffic, heating, and other sources. In contrast to many other risks, exposure to outdoor air pollution occurs during the entire life span. Exposure is variable over time, due primarily to changes in pollutant emissions and weather conditions. Strong evidence indicates that daily variation in exposure to outdoor air pollution correlates with acute exacerbations of COPD (119). In this review, we address the issue of whether outdoor air pollution contributes to pulmonary function impairment and the development of COPD. The related issue of exacerbation of established disease is not further discussed. Technical issues pertinent to methodological and literature search considerations are detailed in Appendix E3.

As of 2001, Sunyer identified several limitations among the existing studies, which were mostly cross-sectional, and considered the evidence regarding outdoor air pollution and COPD inconclusive (119). Sunyer called for larger prospective studies to investigate the role of air pollution in the development of COPD. Subsequently, such studies have been published and comprise the basis of this review with emphasis on longitudinal studies (Table 4).

Lung function in children and young adults. Cross-sectional studies have mostly shown a relationship between higher outdoor pollutant levels and lower lung function (120–125). In addition, two German studies observed that improvements in air quality after reunification were paralleled by better levels of lung function in repeated cross-sectional analyses (126, 127). Another study used black carbon content of sputum macrophages as a biomarker of particulate matter exposure from fossil fuel combustion (125). In this report, higher black carbon content was negatively associated with FEV1.

Several longitudinal studies in children are now available (Table 5). The Southern California Children’s Health Study (CHS) comprises four cohorts that underwent annual lung function measurement up to 8 years of follow-up (128–132). These studies provide strong evidence of an adverse effect of outdoor air pollution on lung function development in children and adolescents. At the end of the follow-up period (age, 18 yr), the percentage of students with low lung function (~80% of normal) was almost five times higher among those who grew up in the most polluted communities compared with the cleanest ones. Further analysis showed that exposure to traffic-related pollution, characterized by the residential distance from a highway, was also associated with poor lung growth and lower lung function achieved at age 18 years (132).

During follow-up, many children moved to other locations throughout the United States and had a change in outdoor air pollution exposure (133). Change in pollution exposure was a significant determinant of lung growth: children moving to cleaner places experienced an increase in lung growth, whereas growth rates decreased among those moving to more polluted areas. Other major cohort studies from Mexico and Europe show that particulate pollution and nitrogen dioxide (NO2), which is a strong marker of traffic-related pollution, are associated with significantly lower pulmonary function growth (134–138).

Lung function and air pollution in adults. In adults, three cross-sectional, three longitudinal, and one case–control study have been published since 2001. Most notably, the German Study on the Influence of Air Pollution on Lung Function, Inflammation, and Aging (SALIA) of 4,575 women is the only one to specify COPD according to GOLD criteria (stage 1 or greater) and to investigate its association with pollution (139). The 5-year mean of particulate matter of less than 10 μm (PM10), measured within 8 km of personal residences, was negatively associated with FVC, FEV1, and FEV1/FVC. Higher PM10 was also related to an increased risk for COPD (odds ratio [OR], 1.33 per 7 μg/m2; 95% confidence interval [CI], 1.03–1.72). Results of the community-based comparison were similar in size than those reported in the Study on Air Pollution and Lung Diseases in Adults (SAPALDIA) (140).

An analysis of the SAPALDIA cohort examined the association between the 11-year change in air quality and lung function decline among 8,047 adult subjects (4,742 had complete follow-up) (141). Because of a broad range of air quality policies implemented in Switzerland, residential PM10 declined over this time period. An 11-year reduction of PM10 by 10 μg/m3 was associated with a decreased rate of annual decline of lung function corresponding to 9% (FEV1), 6% (FEV1/FVC ratio), and 16% (FEF25–75%). Other studies also link outdoor air pollution to lung function in adults (142–144).

Air pollution and objectively defined COPD. Few studies reported results for objectively defined COPD. The previous positive findings of the Adventist Health and Smog (AHSMOG) cohort examined survey-based definitions of chronic bronchitis or emphysema only (145, 146). The German SALIA study of women (see above) specified COPD according to GOLD criteria (stage 1 or greater) (139). Higher PM10 was related to an increased risk for COPD (OR, 1.33 per 7 μg/m2; 95% CI, 1.03–1.72). A nested case–control study based on the Greek component of the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort evaluated subjects for COPD. Case subjects were first identified by questionnaire and verified through a clinical investigation, which included spirometry (147). Black smoke and NO2 data from all monitoring stations were used to estimate exposure for two time periods (past 5 and 20 yr), based on residential and work addresses. The highest exposure quartile (for the most recent 5 yr) was associated with a greater risk of COPD (OR, 2.01; 95% CI, 1.05–3.68). This study is limited by the definition of COPD, which did not require objective evidence of irreversible airway obstruction in all cases.

Air pollution and COPD: conclusions. Longitudinal cohort studies provide strong evidence of an association between outdoor pollution and decreased pulmonary function growth during childhood and adolescence (129, 132, 134). The associ-
### TABLE 4. STUDIES OF OUTDOOR AIR POLLUTION AND LUNG FUNCTION

<table>
<thead>
<tr>
<th>Study (Ref.)</th>
<th>Type of Study</th>
<th>Population and Age Group</th>
<th>Sample Size</th>
<th>Exposure Measurement</th>
<th>Respiratory Outcome Measurement</th>
<th>Adjusted Association, Slope, or Odds Ratio (95% CI or P Value)</th>
<th>Other Findings</th>
<th>Study Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Longitudinal Studies of Children Avol, 2001 (133)</td>
<td>Cohort with &quot;intervention&quot; (due to moving); 5-yr follow-up</td>
<td>“Movers” of two cohorts (enrolled in 1993 at age 10 yr or in 1994 at age 11 yr; follow-up to age 15 yr)</td>
<td>59 boys, 51 girls</td>
<td>Difference in urban background pollution (\text{PM}_{10}, \text{NO}_2, \text{O}_3) at pre- and postmoving residence</td>
<td>Annual growth in (\text{FEV}_1) (ml), MMEF (ml/s), PEF (ml/s)</td>
<td>Per 10(\mu)g/m(^3) increase in (\text{PM}_{10}): (\text{FEV}_1): −6.6 ((-13.3\text{ to }0.3)) MMEF: −16.6 ((-32.1\text{ to }−1.1))</td>
<td>Interpretation: Children moving to cleaner air improved lung function growth; (&quot;to move&quot; can be considered an &quot;exposure intervention&quot;) Similar findings for peak flow</td>
<td>Sample size</td>
</tr>
<tr>
<td>Gauderman, 2000 (131)</td>
<td>Prospective cohort (three age groups); 4-yr follow-up</td>
<td>4th, 7th, and 10th graders recruited in 1993 from schools selected from 12 communities</td>
<td>1,498 4th graders; 802 7th graders; 735 10th graders</td>
<td>Urban background air pollution (central monitors for (\text{PM}<em>{10}, \text{PM}</em>{2.5}, \text{NO}_2, \text{O}_3, \text{O}_3) inorganic acid, elemental carbon)</td>
<td>Annual lung function growth rate (average PFT measurements per child: 3.8)</td>
<td>Annual (\text{FEV}<em>1) growth deficit, 4th grade cohort: (\text{PM}</em>{2.5}) (per 51.5(\mu)g/m(^3) annual mean): −0.85% ((-1.59\text{ to }−0.10)) Predicted 4-yr growth deficit in most polluted area: −3.4%</td>
<td>Similar results for other markers of pollution (e.g., (\text{NO}_2)), asthmatics and nonasthmatics. Similar findings in 7th and 10th graders but not significant</td>
<td>No data on local traffic-related exposures</td>
</tr>
<tr>
<td>Gauderman, 2002 (130)</td>
<td>Prospective cohort (one age group); 4-yr follow-up</td>
<td>4th graders recruited in 1996 from schools selected from 12 communities (mean age, 9.9 yr)</td>
<td>1,678 with at least 2 PFTs, 1996 to 2000</td>
<td>Urban background air pollution (central monitors for (\text{PM}<em>{10}, \text{PM}</em>{2.5}, \text{NO}_2, \text{O}_3, \text{O}_3) inorganic acid, elemental carbon)</td>
<td>Annual lung function growth rate (average PFT measurements per child: 3.8)</td>
<td>All estimates were negative; several reached statistical significance. Annual growth deficits per 22.2 (\mu)g/m(^3) (\text{PM}_{2.5}); (\text{FEV}_1): −0.39% ((-1.06\text{ to }0.28)) MMEF: −0.94% ((-1.87\text{ to }0.0))</td>
<td>Stronger effects in those more outdoors Largely confirms Gauderman, 2000 (131) 4th grade results</td>
<td>No data on local traffic-related exposures</td>
</tr>
<tr>
<td>Gauderman, 2004 (129)</td>
<td>Prospective cohort (one age group); 8-yr follow-up</td>
<td>4th graders recruited in 1993 (same as Gauderman, 2000 [131])</td>
<td>(n = 1,759) with repeated PFT; (n = 747) with tests in 1993 and 2001</td>
<td>Urban background air pollution (central monitors for (\text{PM}<em>{10}, \text{PM}</em>{2.5}, \text{NO}_2, \text{O}_3, \text{O}_3) inorganic acid, elemental carbon)</td>
<td>8-yr growth deficit of (\text{FVC}) (ml), (\text{FEV}_1) (ml), MMEF (ml/s)</td>
<td>8-yr deficit per 22.8 (\mu)g/m(^3) (\text{PM}_{2.5}); (\text{FEV}_1): −79.7 ml ((-153.0\text{ to }−6.4)) MMEF: −168.9 ml ((-345.5\text{ to }7.8))</td>
<td>Estimates for all urban pollutants negative ((\text{FVC}, \text{FEV}_1, \text{MMEF})), mostly statistically significant for (\text{FEV}_1) and MMEF. Similar for the (747) with complete follow-up in most polluted area: (\text{FEV}_1) &lt; 80% at age 18; 7.9% in most polluted area (1.6% in least)</td>
<td>No data on local traffic-related exposures Relationship to future COPD?</td>
</tr>
<tr>
<td>Gauderman, 2007 (122)</td>
<td>Prospective cohort (one age group); 8-yr follow-up</td>
<td>School-based sample from 12 communities; 9-11 yr; 8-yr annual follow-up (1993–2000)</td>
<td>22,686 lung function tests from 3,677 children</td>
<td>Distance: ≤500 m from local freeway Regional pollutants (acid, (\text{NO}<em>2, \text{PM}</em>{10}, \text{PM}_{2.5}))</td>
<td>8-yr growth of (\text{FEV}_1) (and other lung function measures)</td>
<td>Living (&lt; 500) m of freeway vs. (&lt;1,500) m: Growth: (\text{FEV}_1): −81 ml ((-143\text{ to }−18)) Deficit at age 18: (\text{FEV}_1): 97% predicted ((94.6–99.4))</td>
<td>Regional pollutants independently associated with (\text{FEV}_1) growth (confirms Gauderman, 2004 [129]) Similar findings for small airway function For “distance to major roads” no significant results</td>
<td>Not yet clear how “freeway distance” and distance to major roads interact in determining levels of relevant pollutants</td>
</tr>
</tbody>
</table>

(Continued)
<table>
<thead>
<tr>
<th>Study (Ref.)</th>
<th>Type of Study</th>
<th>Population and Age Group</th>
<th>Sample Size</th>
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<th>Other Findings</th>
<th>Study Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Horak, 2002 (136)</td>
<td>Prospective cohort; 3-yr follow-up</td>
<td>2nd and 3rd graders from 8 towns (age, 6–9 yrs); 1994–1997</td>
<td>n = 975 enrolled; n = 860 with follow-up; PFT 2× per yr</td>
<td>Central monitoring data for PM10, NO2, O3, SO2, stratified by summer/winter mean</td>
<td>Annual lung function growth deficit per 10 μg/m3 PM10</td>
<td>FEV1: −84 ml/yr (p = 0.003) MMEF: −329 ml/s/yr (p &lt; 0.001)</td>
<td>Winter PM10 also significantly associated with FEV1 growth</td>
<td>Short follow-up; seasonal analyses; partly inconsistent with findings from same cohort with 1 yr fewer data (Frischer et al., 1999 [138])</td>
</tr>
<tr>
<td>Rojas-Martinez, 2007 (134)</td>
<td>Prospective cohort; 3-yr follow-up</td>
<td>Children (age 8 yr) from 39 randomly selected schools near to monitors; 1996–1999</td>
<td>n = 3,170 enrollees; PFT 2× per yr</td>
<td>Central monitor data close to school: PM10, NO2, O3</td>
<td>Annual lung function growth, per IQR of pollutant</td>
<td>Annual growth per 36.4 μg/m3 PM10; Girls: FEV1: −29 ml (−36 to −21); FEF25–75: −17 ml/s (−36 to 1); Boys: FEV1: −27 ml (−34 to −19); FEV1: −25–75: −18 ml/s (−34 to −2)</td>
<td>PM10, NO2, and O3 associated (mostly significant) with growth deficits of FVC, FEV1, and FEF25–75, in boys and girls. Effect on FVC stronger, thus FEV1/FVC positively associated with pollution</td>
<td>Relatively short follow-up; no local traffic-related pollution measurements</td>
</tr>
<tr>
<td>Holguin, 2007 (124)</td>
<td>Panel study, analyzed by cross-sectional analysis of lung function data (4-mo repeated measurements)</td>
<td>6–12 yr; school-based sample (asthmatic and nonasthmatic)</td>
<td>n = 194 (95 asthmatic, 99 nonasthmatic)</td>
<td>GIS model for NO2 and EC at school; school road density; home road density</td>
<td>IQR increase in road density within 50–100, 200–500 m buffer</td>
<td>FEV1 per IQR density in 3 distance buffers: 50 m: −91 ml (−174 to −7); 100 m: −72 ml (−134 to −9); 200 m: −106 ml (−171 to −41)</td>
<td>Exhaled NO also associated with traffic</td>
<td>Findings restricted to asthmatics; no associations in nonasthmatics Small sample Analysis of panel data was cross-sectional</td>
</tr>
<tr>
<td>Gotschi, 2008 (294)</td>
<td>Prospective follow-up and cross-sectional analyses; ~10-yr follow-up</td>
<td>Random population samples from 20 cities in 10 countries, age 20–44 yr at baseline (1991–1993); follow-up 2000–2002</td>
<td>4,290 with complete data</td>
<td>Annual mean from 1 single monitor per city (PM10)</td>
<td>Level of lung function (FVC, FEV1, FEF25–75)</td>
<td>Unadjusted model: Negative associations with FEV1 and FVC; adjusted models show no associations with PM2.5 or other background pollutants</td>
<td>Strong correlation between city-level pollution and height and other covariates with north-south gradients</td>
<td>Local traffic-related exposure data among a small subsample suggest very large exposure misclassification in this cross-community analysis</td>
</tr>
<tr>
<td>Longitudinal Studies of Adults Selke, 2004 (144)</td>
<td>Cohort; 8-yr follow-up (1987–1994)</td>
<td>Population sample of adult women age 30–59 yr, living ≥1 yr in same exposure area</td>
<td>Total: 733 women; n = 406 with PFT follow-up data</td>
<td>Distance to busy road, three groups: A: &lt; 20 m from busy road (47–56 ppb NO2); B: 20–150 m (38–46 ppb NO2); C: “behind roads” (24–36 ppb NO2)</td>
<td>Adjusted change in FVC, and FEF25–75</td>
<td>ΔFEV1 per yr: A: −20 ml B: −15 ml C: −9 ml P for trend &lt; 0.001 translates roughly to a 5–ml faster decline per yr per 11 ppb NO2</td>
<td>Similar trend for FVC but not statistically significant</td>
<td>Only three comparison areas; those were, however, selected on the basis of traffic-related pollution</td>
</tr>
<tr>
<td>Downs, 2007 (141)</td>
<td>Cohort; 11-yr follow-up</td>
<td>Population sample of adults from 8 cities; age 18–60 yr at baseline, 1991</td>
<td>n = 4,742 with follow-up data (2002)</td>
<td>11-yr change in lung function vs. change in pollution</td>
<td>Adjusted decline in lung function</td>
<td>Per 10 μg/m3 reduction in PM10 decline in FEV1 reduced by 3 ml (0.03–6.2) (~9% of mean decline). Decline in FEV1/FVC reduced by 0.06% (0.01–0.12)</td>
<td>Stronger effects in never-smokers</td>
<td>Not analyzed for GOLD-defined COPD</td>
</tr>
</tbody>
</table>

(Continued)
ation observed between black carbon content in respiratory tract macrophages and decreased pulmonary function provides biological plausibility for the role of air pollution in decreased pulmonary function development (125). Therefore, there is adequate evidence of an association between outdoor pollution and reduced pulmonary function.

Table 4 includes longitudinal studies of children, longitudinal studies of adults, and cross-sectional studies of adults that include the FEV<sub>1</sub>/FVC ratio or objectively defined COPD. Only studies published since the review by Sunyer (119) are included.

Because there are fewer studies that defined COPD by spirometry, there is limited/suggestive evidence of a relationship between outdoor air pollution and COPD. To the extent that decreased lung function growth early in life translates into a greater incidence of COPD in later adulthood, the likelihood of a true association between air pollution and COPD is higher. Moreover, there is no local traffic-related pollution data.

**Figure 2.** Secondhand smoke (SHS) exposure and the risk of COPD. Forest plot shows studies of SHS exposure and the risk of chronic obstructive pulmonary disease. Summary odds ratio was derived from meta-analysis with random effects model. CI = confidence interval; OR = odds ratio.

**Definition of abbreviations:** COPD = chronic obstructive pulmonary disease; EC = elemental carbon; GIS = geographic information system; GOLD = Global Initiative for Chronic Obstructive Lung Disease; IQR = interquartile range; MMEF = maximal mid-expiratory flow; n.s. = not significant; OR = odds ratio; PEF = peak expiratory flow; PFT = pulmonary function test; PM<sub>10</sub>, PM<sub>2.5</sub> = particulate matter of less than 10 and 2.5 μm, respectively.
of pulmonary function over time and COPD. These mechanisms could produce irreversible loss of pulmonary function over time and COPD.

**Secondhand Smoke Exposure and the Risk of COPD**

Exposure to secondhand smoke (SHS), which contains potent respiratory irritants, may lead to chronic airway inflammation and obstruction. Although SHS exposure appears to cause asthma in children and adults, its role in causing COPD has received less attention in epidemiologic studies (149).

A body of literature now supports an association between SHS exposure and the development of COPD independent of personal cigarette smoking (Table E5 and Figure 2). Studies support a link between SHS exposure and self-reported chronic bronchitis, emphysema, or COPD (29, 150–158). In particular, a population-based study showed that both cumulative home and workplace SHS exposure were associated with a greater risk of self-reported physician-diagnosed COPD (150).

A study from China found that self-reported cumulative lifetime SHS exposure at home and work was related to a greater risk of COPD, as defined by spirometry (GOLD stage 1 or greater) (158). Another study showed that living with a smoker was associated with a greater risk of a physician diagnosis of COPD (157).

The 15-year follow-up from the AHS-MOG study, which was a population-based study of Seventh Day Adventists principally residing in Southern California, found a relationship between ever having SHS exposure and a greater risk of spirometrically defined airway obstruction (159). Other publications from this study have reported a link between SHS and “obstructive lung disease,” but a composite definition was used that included asthma in addition to chronic bronchitis, emphysema, and “COPD” (153, 160). Other longitudinal data from SAPALDIA showed that baseline SHS exposure was associated with a greater prospective incidence of chronic bronchitis symptoms and a lower likelihood of remission among those who were previously symptomatic (155).

Studies of bar and hospitality workers who were heavily exposed to SHS in the workplace indirectly address the issue of SHS as a possible cause of COPD. After laws prohibiting smoking have been implemented, hospitality workers experienced a substantial reduction in cough and phlegm and an improvement in pulmonary function (161–167). Other studies show that hospitality workers can experience a substantive decrement in spirometry after a single work shift in a smoky environment, suggesting that SHS has acute negative effects on pulmonary function (166, 168). In addition, the cross-shift reduction of pulmonary function improved after a workplace smoking ban reduced SHS exposure (169, 170). Taken together, this evidence supports the plausibility of SHS exposure as a risk factor for COPD.

**SHS smoke and COPD: conclusions.** Review of the evidence indicates limited/suggestive evidence of an association between SHS exposure and development of COPD. The association between SHS and COPD is consistent and coherent among various case definitions (e.g., airway obstruction, physician diagnosis). The temporal relationship has been established in studies evaluating cumulative lifetime exposure. An exposure–response gradient was demonstrated in several studies. Biological plausibility is supported by the presence of numerous airway irritants contained in tobacco smoke and the strong relationship between direct smoking and COPD.

**Biomass Smoke and the Risk of COPD**

In developing countries, a significant proportion of COPD cases occurs among never-smokers, especially in women cooking with open fire stoves. The fuel used in these stoves is collectively known as biomass, which includes wood, animal dung, and crop residues. These stoves emit high levels of multiple pollutants that are similar to those present in tobacco smoke (171).

Approximately half of the world’s population uses solid fuels for cooking; usage is even higher in rural areas (up to 80%). Particulate matter concentrations in these kitchens are very high, with average values in the range of milligrams per cubic meter and peak levels ranging 10–30 mg/m³ (171). These levels greatly exceed most governmental standards for outdoor air.

In many developing countries, biomass smoke exposure occurs during the entire life span. It begins in utero and continues during infancy when exposure may impair lung defense mechanisms and may lead to respiratory infections and tuberculosis. In childhood and adulthood, females continue to have direct exposure while cooking or helping in the kitchen. Consequently, biomass smoke exposure may affect the growth of lung function, development of peak lung function, and the normal decline of function that begins in early adulthood (Figure 1).

The first studies that documented chronic lung disease and cor pulmonale among people cooking with open fire stoves considered a role for repeated respiratory infections, bronchiectasis, and lung scarring due to tuberculosis (172–176). However, most patients who are diagnosed with biomass-related COPD, in the absence of personal cigarette smoking, lack significant bronchiectasis and scarring. Such patients may develop COPD with cor pulmonale (177–179) and have a shortened life span (180).

Several case–control and cross-sectional studies have found a consistent association between cooking with biomass stoves and respiratory symptoms, chronic bronchitis, and chronic airflow obstruction (179, 181–186). Use of solid fuel stoves was usually estimated from questionnaires; exposure was often measured as present or absent or by daily hours spent by the stove. Most studies did not include direct measurements of specific pollutants. Studies that have measured kitchen particulate levels from biomass fuel use have confirmed high concentrations (181, 191), but personal measurements of exposure have not been used in most epidemiologic studies.

Reported case–control studies consistently found an association between cooking with biomass stoves and chronic bronchitis or airflow obstruction (186, 188, 190, 197, 198). These studies are mostly from developing countries, with the exception of a study from Spain (198). These studies report a strong association between cooking with biomass stoves and COPD among female never-smokers (Table E6 and Figure 3), with evidence of an exposure–response relationship (e.g., hours of cooking per day and number of years cooking with biomass).

Exposure to biomass smoke is clearly associated with respiratory symptoms and chronic bronchitis in cross-sectional studies (181–184, 188, 189, 191–195, 199, 200); other studies have also found decreased pulmonary function among women cooking with biomass fuels (Table E6) (191, 201–204). For example, a study from rural Mexico found that biomass use was associated with a 4% decrease in FEV1/FVC (191). In addition, an increase in the level of particulate matter concentration of 1,000 µg/m³ was associated with a 2% reduction in FEV1. A study from Colombia found that biomass stove use for 10 or more years was associated with a greater risk of COPD as defined by a postbronchodilator FEV1/FVC ratio less than 0.70 (GOLD stage 1 or greater; OR, 1.5; 95% CI, 1.22–1.86) (205).

Limited experimental evidence of lung damage due to biomass smoke has been published (206, 207). In one study, rats...
exposed intermittently to wood smoke for 75 minutes daily for 15 days had mononuclear bronchiolitis and mild emphysema, which was more severe in animals exposed for 30 and 45 days (207). Soft coal or “smoky coal,” which is more polluting than other biomass, is used as fuel in parts of China and India. In China, such smoky coal use for cooking was associated with the diagnosis of COPD (208). In addition, use of an improved vented coal stove considerably reduced the incidence of COPD (209).

**Biomass and COPD: conclusions.** There is sufficient evidence of an association between burning of biomass fuel and the development of COPD in women. The evidence is inadequate to infer the presence or absence of a causal relationship in men because they are typically not exposed at high levels over a long time period; men have also not been systematically studied. In women, there are multiple studies that have consistently linked biomass smoke exposure with chronic bronchitis and COPD defined by spirometry. There is experimental evidence supporting biological plausibility and evidence of exposure–response.

### Occupational Exposure and the Risk of COPD

COPD does not have a clinical subcategory that is clearly identified as occupational, largely because the condition develops slowly and, given that the airway obstruction is chronic, does not reverse when exposure is discontinued. Consequently, a diagnosis of “occupational COPD” is rarely made by clinicians; this situation is in sharp contrast to occupational asthma, which is more frequently recognized.

The demonstration of an association between occupational exposures and COPD in epidemiological studies can be difficult because of several factors. First, COPD is multifactorial in etiology, with critical (and mostly unknown) host as well as nonoccupational environmental determinants of risk. Second, unlike workers with pneumoconioses, individuals with COPD due to occupational exposures cannot be distinguished from those with the disease due to other causes. Third, many workers with COPD have concurrent exposure to cigarette smoke (direct and/or secondhand smoke) and workplace irritants. Fourth, exposed workers at baseline tend to have better overall health and pulmonary function than the general population, the so-called healthy worker effect. Fifth, workforce studies are often limited to a “survivor” population because of inability to assess or monitor workers who leave their jobs, thereby underestimating the chronic effects of occupational exposures.

Despite these difficulties, an impressive body of literature accumulated over the past two decades demonstrates the link between specific occupational exposures and the development of COPD. Longitudinal studies of the effects of occupational exposures and COPD have been performed in coal miners (210–213), hard-rock miners (214, 215), tunnel workers (216), concrete-manufacturing workers (217), and nonmining industrial workers in Paris (218). In these studies, moderate smoking and occupational exposures had approximately comparable effects on COPD risk.

Quantitative pathological assessment of emphysema as an outcome variable has confirmed a relationship between dust exposure and degree of emphysema in several studies of coal and hard-rock miners (219–223). The relationship is stronger among smokers than nonsmokers and easier to demonstrate when coal dust–induced fibrosis is present.

Perhaps the strongest evidence implicating occupational exposures in the pathogenesis of COPD comes from community-based studies (Table 5). Although these studies were typically not designed to examine the relationship of occupational exposures to COPD, they nonetheless yielded evidence of such a relationship. A major advantage of community-based studies is that the problem of survivor bias is largely avoided. Community-based studies from China, France, Italy, the Netherlands, New Zealand, Norway, Poland, Spain, and the United States have demonstrated increased relative risks for respiratory symptoms and/or chronic airflow limitation consistent with COPD as well as for excess annual decline in FEV1 associated with occupational exposure to dusts, gases, and fumes (224–238). The concordance of findings from studies using self-reported occupational exposures and a job exposure matrix (assigned probability of exposure based on job type or duties) supports a causal role for workplace exposures in COPD causation.
TABLE 5. COMMUNITY-BASED STUDIES OF OCCUPATIONAL EXPOSURE AND RISK OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE

<table>
<thead>
<tr>
<th>Study (Ref.)</th>
<th>Type of Study</th>
<th>Population</th>
<th>Sample Size</th>
<th>Exposure Measure</th>
<th>Respiratory Outcome Measure</th>
<th>Adjusted Odds Ratio (95% CI or P Value)</th>
<th>Other Findings</th>
<th>Study Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rom et al., 1987 (233)</td>
<td>Cross-sectional cohort</td>
<td>Population study of six cities in the United States</td>
<td>8,515 subjects</td>
<td>Self-report of occupational exposure to dusts, gases/fumes</td>
<td>FEV1/FVC &lt;60%</td>
<td>1.53 (1.17–2.08)</td>
<td>Or for chronic respiratory symptoms, 1.27–1.60</td>
<td>Potential exposure misclassification</td>
</tr>
<tr>
<td>Viegi et al., 1991 (231)</td>
<td>Cross-sectional cohort</td>
<td>Population study of Po delta area in northern Italy</td>
<td>763 male subjects</td>
<td>Self-report of occupational exposure to dusts, gases, and fumes</td>
<td>FEV1/FVC &lt;70%</td>
<td>1.45</td>
<td>Or for chronic cough and phlegm, 1.69 and 1.64</td>
<td>Potential exposure misclassification</td>
</tr>
<tr>
<td>Fishwick et al., 1997 (225)</td>
<td>Cross-sectional cohort</td>
<td>Population study of four areas in New Zealand (ECRHS)</td>
<td>1,132 subjects</td>
<td>Self-report of occupational exposure to dusts, gases, and fumes</td>
<td>FEV1/FVC &lt;75% and chronic bronchitis symptoms</td>
<td>3.13 (1.07–9.12)</td>
<td>Or for bakers and spray painters, 25.5 and 14.4, respectively</td>
<td>Potential exposure misclassification</td>
</tr>
<tr>
<td>Sunyer et al., 1998 (235)</td>
<td>Cross-sectional cohort</td>
<td>Population study of five areas in Spain (ECRHS)</td>
<td>1,735 subjects</td>
<td>Self-report of occupational exposure to dusts, gases, and fumes</td>
<td>FEV1/FVC &lt;70%</td>
<td>3.0 (1.0–9.4)</td>
<td>For high mineral dust exposure</td>
<td>Potential exposure misclassification</td>
</tr>
<tr>
<td>Kryzanowski et al., 1986 (228)</td>
<td>Longitudinal cohort</td>
<td>Population study of Cracow, Poland</td>
<td>1,824 subjects</td>
<td>Self-report of occupational exposure to dusts</td>
<td>Rate of decline in FEV1</td>
<td>Accelerated decline in FEV1, with exposure to dusts</td>
<td>Potential exposure misclassification</td>
<td></td>
</tr>
<tr>
<td>Humerfelt et al., 1993 (226)</td>
<td>Longitudinal cohort</td>
<td>Population study of Bergen, Norway</td>
<td>951 subjects</td>
<td>Self-report of occupational exposures to 11 airborne agents (dusts, gases, vapors, and fumes)</td>
<td>Rate of decline in FEV1</td>
<td>Accelerated decline in FEV1 with exposure to sulfur dioxide gas and to metal fumes</td>
<td>Increased adjusted decline in FEV1 in subjects exposed to increasing numbers of occupational agents (test for trend; P &lt; 0.01)</td>
<td>Potential exposure misclassification</td>
</tr>
<tr>
<td>Bakke et al., 1991 (224)</td>
<td>Cross-sectional cohort</td>
<td>Population study in Norway</td>
<td>1,512 subjects</td>
<td>Self-report of occupational exposures to 11 airborne agents (dusts, gases, vapors, and fumes)</td>
<td>Airflow limitation (FEV1/FVC &lt;0.70 and FEV1 &lt;80% of predicted)</td>
<td>Occupational exposures to quartz and asbestos dust were associated with airflow limitation</td>
<td>Or for obstructive lung disease (asthma or chronic obstructive lung disease), 3.6 (1.3–9.9) for high occupational exposure to airborne agents</td>
<td>Potential exposure misclassification</td>
</tr>
<tr>
<td>Xu et al., 1992 (232)</td>
<td>Cross-sectional cohort</td>
<td>Population study in Beijing, China</td>
<td>3,606 subjects</td>
<td>Self-report of occupational exposure to dusts, gases/fumes</td>
<td>FEV1, FEV1/FVC, FEF25–75</td>
<td>Dust exposure was associated with decreased FEV1, FEV1/FVC, and FEF25–75, gas/fume exposure with decreased FEV1 and FVC</td>
<td>Or for chronic respiratory symptoms, 1.30 (1.09–1.48) for dusts and 1.27 (1.09–1.48) for gases/fumes</td>
<td>Potential exposure misclassification</td>
</tr>
<tr>
<td>de Meers et al., 2001 (247)</td>
<td>Cross-sectional cohort</td>
<td>Dutch population study (ECRHS)</td>
<td>1,906 subjects</td>
<td>Job-exposure matrix</td>
<td>FEV1, FEV1/FVC</td>
<td>Organic dust exposure was associated with decreased FEV1, −63 ml (−118, −8); mineral dust exposure with decreased FEV1/FVC, −1.11% (−1.8, −0.3)</td>
<td>Or for chronic bronchitis for mineral dust exposure, 2.22 (1.16–4.23)</td>
<td>Potential exposure misclassification</td>
</tr>
</tbody>
</table>

(Continued)
A previous American Thoracic Society statement estimated that the population-attributable fraction (PAF) for the workplace contribution to COPD risk is approximately 15%–20% (239). Ten articles that were published before 2000 had sufficient data to calculate a PAF; several of the articles presented data supporting a greater than 20% PAF for respiratory symptoms and lung function impairment due to work-related factors.

Since 2000, multiple additional articles have provided further evidence in support of a major contribution of occupational exposures to the burden of COPD (Table 5). One review reported the PAF for occupational exposures that was derived from another 14 separate studies (35, 240–252). On the basis of these data, the median PAF value for workplace exposures for both chronic bronchitis and COPD was 15% (253). Many additional studies published since 2000 underscore the association between specific occupational exposures and airway obstruction (236–238, 254–259).

Biological plausibility of the reported associations between occupational exposures to airway irritants and COPD is supported by inhalational toxicological studies. Several agents known to be associated with clinically defined chronic bronchitis in humans (e.g., endotoxin, mineral dusts, sulfur dioxide, and vanadium) have been shown to be capable of inducing pathologically defined chronic bronchitis in animal models (260–263). Agents for which occupational exposure occurs that can cause emphysema in animals includes cadmium, coal, endotoxin, and silica (264). The biological plausibility of an occupational exposure–COPD association is also supported by data from two studies of individuals with severe deficiency of α1-antitrypsin (52, 265). Occupational exposure to dusts, gases, and vapors, mineral dust, and metal dust most associated with COPD (Table 5). One review reported the PAF for occupational exposures that was derived from another 14 separate studies (35, 240–252). On the basis of these data, the median PAF value for workplace exposures for both chronic bronchitis and COPD was 15% (253). Many additional studies published since 2000 underscore the association between specific occupational exposures and airway obstruction (236–238, 254–259).

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Table 5. (Continued)

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<th>Study (Ref.)</th>
<th>Type of Study</th>
<th>Population</th>
<th>Sample Size</th>
<th>Exposure Measure</th>
<th>Respiratory Outcome Measure</th>
<th>Adjusted Odds Ratio (95% CI or P Value)</th>
<th>Other Findings</th>
<th>Study Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jaen et al., 2002 (240)</td>
<td>Cross-sectional cohort</td>
<td>Population study of an urban-industrial area of Catalonia, Spain</td>
<td>497 subjects</td>
<td>Self-reported occupational exposure to dusts, gases, and fumes</td>
<td>FEV1, FEV1/FVC, FEV25–75</td>
<td>&gt;15-yr exposure to dusts, gases, or fumes associated with decreased FEV1, –80 ml (–186, –26); FEV1/FVC, –1.7% (–3.3, –0.2); FEV25–75, –163 ml (–397, –71)</td>
<td>Potential exposure misclassification</td>
<td></td>
</tr>
<tr>
<td>Hnizdo et al., 2002 (250)</td>
<td>Cross-sectional cohort</td>
<td>NHANES III population study in the USA</td>
<td>9,823 subjects</td>
<td>Self-report of longest job and standard coding of occupation and industry</td>
<td>COPD (FEV1/FVC &lt;0.70 and FEV1 &lt;80% of predicted)</td>
<td>ORs for COPD increased for multiple occupations and industries</td>
<td>Fraction of COPD attributable to work was estimated as 19.2% overall and 31.1% among never-smokers</td>
<td>Potential exposure misclassification</td>
</tr>
<tr>
<td>Matheson et al., 2005 (243)</td>
<td>Cross-sectional cohort</td>
<td>Population study in Australia</td>
<td>1,232 subjects</td>
<td>Self-report of longest job and standard coding of occupation; job-exposure matrix</td>
<td>COPD (FEV1/FVC &lt;0.70 with either chronic sputum production or DlCO &lt;80% predicted and dyspnea)</td>
<td>2.70 (1.39–5.23) for biological dust exposure</td>
<td>OR for FEV1/FVC &lt;0.70 with chronic sputum production for gases and fumes exposure, 2.81 (1.01–7.79)</td>
<td>Potential exposure misclassification</td>
</tr>
<tr>
<td>Boggia et al., 2008 (237)</td>
<td>Prospective cohort</td>
<td>Population-based work surveillance program in Italy</td>
<td>2,734 males</td>
<td>Self-report of vapor, dust, or fumes with expert review of job classification for confirmation</td>
<td>COPD (classic chronic bronchitis plus FEV1/FVC &lt;0.70 and FEV1 &lt;80% predicted)</td>
<td>Occupational exposure OR, 2.62 (2.02 to 3.41)</td>
<td>Combined effects of smoking and occupation found</td>
<td>Potential exposure misclassification; very conservative definition of COPD; males only</td>
</tr>
<tr>
<td>Weinmann et al., 2008 (236)</td>
<td>Case control</td>
<td>Kaiser Permanente Northwest</td>
<td>388 COPD case subjects, 356 matched control subjects</td>
<td>Self-reported occupational exposure plus expert review</td>
<td>COPD diagnosis based on validated algorithm</td>
<td>Diesel exhaust, irritant gases and vapors, mineral dust, and metal dust most associated with COPD</td>
<td>Not all subjects had spirometry; potential exposure misclassification*</td>
<td></td>
</tr>
<tr>
<td>Blanc et al., 2008 (238)</td>
<td>Case-control</td>
<td>Kaiser Permanente Northern California health plan members</td>
<td>1,202 adults with COPD, 302 matched control subjects</td>
<td>Self-reported VDGF on longest held job; job-exposure matrix</td>
<td>COPD (by health care use); subset with GOLD stage 2 or greater</td>
<td>VDGF; OR, 2.11 (1.59 to 2.82) Highest JEM category vs. lowest: OR, 2.27 (1.46 to 3.52)</td>
<td>Joint exposure to both smoking and VDGF markedly increased the risk of COPD (OR, 14.1; 95% CI, 9.33–21.2)</td>
<td>Younger patients with COPD (age, 45–65 yr); all health plan members</td>
</tr>
</tbody>
</table>

Definition of abbreviations: CI = confidence interval; COPD = chronic obstructive pulmonary disease; DlCO = diffusing capacity of the lung for carbon monoxide; ECRHS = European Community Respiratory Health Survey; GOLD = Global Initiative for Chronic Obstructive Lung Disease; JEM = job-exposure matrix; NHANES III = Third National Health and Nutrition Examination Survey; OR = odds ratio; VDGF = diffusing capacity of the lung for carbon monoxide.
<table>
<thead>
<tr>
<th>Reference</th>
<th>Type of Study</th>
<th>Population</th>
<th>Sample Size</th>
<th>Exposure Assessment</th>
<th>Respiratory Outcome</th>
<th>Other Findings</th>
<th>Study Limitations-Comments</th>
</tr>
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<tr>
<td>Vitamin E Schunemann et al., 2002 (268)</td>
<td>Cross-sectional, USA, 1995–1998</td>
<td>Random sample from general population of northern USA</td>
<td>1,616 adults, 35–79 yr</td>
<td>6.9 mg/d</td>
<td>FEV₁, 1.29% increase from predicted value (0.16–2.41) FVC, NS</td>
<td>No effect of vitamin C after stratification by smoking: effect only in never-smokers FEV₁, 1.58% (0.008, 3.14) FVC, 1.96% (0.37, 3.35)</td>
<td>Adjusted for potential confounding variables including smoking and other antioxidants</td>
</tr>
<tr>
<td>Hu and Cassano, 2000 (295)</td>
<td>Cross-sectional</td>
<td>(NHANES III), USA, 1988–1994</td>
<td>18,162 adults, &gt;17 yr (NHANES III)</td>
<td>9.1 mg/d</td>
<td>FEV₁, 16.4 ml (5.5–27.4)</td>
<td>Interaction with smoking, larger effect among former smokers (21.9; 95% CI, 2.6, 41.3) and current smokers (20.4; 95% CI, 7.8, 32.7) vs. 11.7 (–0.6, 24.1) in nonsmokers</td>
<td>Serum levels positively related with FEV₁ effect observed among nonsmokers, former and current smokers</td>
</tr>
<tr>
<td>Butland et al., 2000 (296)</td>
<td>Prospective cohort study with cross-sectional and longitudinal analysis</td>
<td>Sample of Welshmen aged 45–59 yr</td>
<td>2512 men, 45–59 yr</td>
<td>2.0 mg/d</td>
<td>FEV₁, 39 ml (95% CI, 6–69)</td>
<td>No significant effect of vitamin C, β-carotene, and magnesium intake</td>
<td></td>
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<tr>
<td>β-Carotene and Retinol Sharp et al., 1994 (297)</td>
<td>Cross-sectional</td>
<td>Population-based part of ARIC cohort study</td>
<td>10,416 middle-aged adults</td>
<td>Dietary vitamin A, lowest vs. highest</td>
<td>FEV₁/FVC &lt;65% OR, 1.1 (0.6–1.9)</td>
<td>Vitamin A protective in heavy current smokers in the upper tertile of cigarette smoke (&gt;41 pack-years)</td>
<td>Adjusted for potential confounding variables including smoking</td>
</tr>
<tr>
<td>Grievink et al., 1998 (298)</td>
<td>Cross-sectional; The Netherlands, 1994–1995</td>
<td>6,555 adults, 20–59 yr</td>
<td>2.5 mg/d</td>
<td>FEV₁, 66 ml (31.4–88.6) FVC, 75.5 ml (40.2–110.2)</td>
<td>Inconsistent results across studies</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hu and Cassano, 2000 (295)</td>
<td>Cross-sectional (NHANES III), USA 1988–1994</td>
<td>18,162 adults ≥17 yr (NHANES III)</td>
<td>1,017 retinol equivalent (RE)</td>
<td>FEV₁, 18.2 (8.7–27.6)</td>
<td>Interaction with smoking, greater effect in nonsmokers (22.4; 95% CI, 8.9, 35.8) vs. smokers (2.9; 95% CI, –14.9, 20.7)</td>
<td>Serum levels positively related with FEV₁ effect observed among nonsmokers and former smokers</td>
<td></td>
</tr>
<tr>
<td>Chen et al., 2001 (299)</td>
<td>Cross-sectional, Scottish</td>
<td>MONICA survey, 1995; random sample from general practitioner list</td>
<td>865 men and 971 women, 25 to 64 yr</td>
<td>100 µg/d</td>
<td>In men: FEV₁, NS FVC, 7.3 ml (3, 3.1 ml) No significant effects in women</td>
<td>Adjusted for potential confounding variables including smoking and waist circumference</td>
<td></td>
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<tr>
<td>Other Carotenoids Schunemann et al., 2002 (268)</td>
<td>Cross-sectional, USA, 1995–1998</td>
<td>Random sample from general population of northern USA</td>
<td>1,616 adults, 35–79 yr</td>
<td>1,825 µg/d lutein/xanthin</td>
<td>FEV₁, 1.7% increased from predicted value (0.8–2.6)</td>
<td>Interaction with smoking, greater effect in current smokers FEV₁, 2.54 (95% CI, 0.14, 4.94) FVC, 2.5% (95% CI, 0.53, 4.63)</td>
<td>Adjusted for potential confounding variables including smoking and other antioxidants</td>
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(Continued)
Diet and the Risk of COPD

Nutrition may affect the development and maintenance of lung function and could modulate pulmonary responses to injury. Consequently, diet could be a factor in the development of COPD. In particular, oxidative stress may contribute to the pathogenesis of COPD. A disturbed balance between oxidants and antioxidants, with an increased oxidant burden, could predispose to COPD. Conversely, a diet high in antioxidants could be protective (266).

Vitamin C, vitamin E, carotenoids, and other antioxidants. More epidemiological evidence has accumulated for the beneficial effect of vitamin C on lung function than on any other individual nutrient (Table E7). Cross-sectional studies have consistently shown that subjects consuming high levels of vitamin C have a greater FEV\textsubscript{1} than those consuming lower levels. Only one longitudinal study has demonstrated a relationship between higher vitamin C intake and a reduced decline in FEV\textsubscript{1} during a 9-year period (267).

Other antioxidants, including vitamin E, carotenoids, and flavonoids, have also been evaluated. Greater FEV\textsubscript{1} has been reported in association with higher vitamin E; however, results are less consistent across studies. β-Carotene intake has been positively related to lung function in cross-sectional studies (261, 262). Lutein/zeaxanthin intake has also been associated with better pulmonary function (263, 268, 269). Another study suggests the beneficial impact of a high intake of catechin (a flavonoid) on pulmonary function and chronic respiratory symptoms (Table 6) (264).

Other studies have used serum levels as marker of vitamin intake including vitamin C, Vitamin E, β carotene, other carotenoids, and selenium. Cross-sectional studies of serum vitamin C levels have consistently supported a positive association between vitamin C serum levels and lung function (Table E8) (52). Results are also consistent for other antioxidants...
A longitudinal analysis of the European Community Respiratory Health Survey (ECRHS) further showed that an increase of 0.5 μmol of β-carotene per liter between two surveys (8 yr apart) was associated with a lower decline in FEV₁ (reduced by 25.5 ml/yr) (272).

**Fruit and vegetable intake.** Some foods are rich in antioxidant nutrients, such as fruits and vegetables (Table E9). Fruit consumption has been positively related to lung function (273). In a prospective study, investigators found that changes in, rather than average levels of, fresh fruit consumption were predictive of changes in FEV₁ over a 7-year time period (274). Notably, a decrease in consumption was associated with a decline in FEV₁. In a 25-year prospective study, the intake of fruit, particularly solid fruits such as apples and pears, was inversely related to the incidence of chronic lung diseases including asthma, bronchitis, and emphysema (275).

**Randomized trials of vitamin supplementation.** Two randomized placebo-controlled trials evaluated the impact of β-carotene and retinyl palmitate (CARET [β-Carotene and Retinol Efficacy Trial]) and of β-carotene and α-tocopherol (ATBC [α-Tocopherol β-Carotene Cancer Prevention] trial) on the risk of cancer (Table E10) (268, 269, 276, 277). Neither study met inclusion criteria for this review because they studied only smokers (CARET had 99.3% smokers, and ATBC had 100% smokers). Nonetheless, it is important to acknowledge that the CARET study showed no impact of supplementation on the rate of decline of lung function during its 11-year follow-up; there was no specific assessment of COPD as a study end point. The ATBC trial found no impact of supplementation on the incidence of chronic bronchitis. Both studies found increased lung cancer among subjects receiving supplementation. In addition, the Medical Research Council/British Heart Foundation (MRC/BHF) Heart Protection Study found no impact of vitamin supplementation with vitamin E, vitamin C, and β-carotene on FEV₁ at the 5-year follow-up time point; there was no specific evaluation for COPD (276, 277). Although the trial included nonsmokers, all subjects had preexisting vascular disease or diabetes.

**Omega-3 polyunsaturated fatty acids and fish intake.** Some cross-sectional studies have shown a protective effect of omega-3 fatty acids or fish intake on COPD or lung function among past or current smokers (270, 271), whereas others have found no effect (272, 273). The only prospective cohort study observed no protective effect of omega-3 fatty acids on the risk of chronic nonspecific lung disease after adjusting for other nutrients (Tables 6 and E8) (275).

*Vitamin D.* Vitamin D has attracted attention because of its potential effect on tissue remodeling (278). Analysis of serum vitamin D levels (25-hydroxyvitamin D) from the Third National Health and Nutrition Examination Survey (NHANES III) study found that the greatest quintile of vitamin D was associated with higher mean FEV₁ and FVC compared with the lowest quintile (Table E8) (278).

**Food with deleterious effects.** Cured meat (bacon, hot dogs, and processed meat such as sausage, salami, and cured ham) contains preservatives such as nitrates that can generate reactive nitrogen species and amplify pulmonary inflammation (279). An analysis of the NHANES III study found that higher cured meat consumption was associated with a lower FEV₁ and a greater risk of self-reported diagnosis of COPD (280). Other studies corroborate these findings (281).

**Diet and COPD: conclusions.** Observational studies strongly suggest that dietary factors, such as a higher intake of vitamin C and other antioxidants, are significantly associated with better lung function and attenuated decline. Consistency of the association across studies and methodologies (food frequency questionnaires or serum vitamin levels) adds strength to the likelihood of a causal association.

Studies on diet and pulmonary function are subject to limitations. Dietary consumption, whether measured by survey or serum vitamin levels, reflects recent intake and does not necessarily reflect cumulative intake or past intake (282). Because pulmonary function impairment develops during a longer time period, the shorter term dietary assessment cannot be clearly linked with pulmonary function decline. A “healthier” diet may also be associated with other aspects of a healthy lifestyle that may confound the relation between diet and COPD risk. Although most studies controlled statistically for smoking, it may still confound the results because smokers may have poorer diets. Although the randomized trials do not suffer from these limitations, the CARET and ATBC studies did not study nonsmokers and therefore do not directly address the genesis of nonsmoking COPD. Moreover, the CARET and MRC/BHF Heart Protection Study did not include a specific COPD endpoint.

Taken together, there is limited/suggestive evidence of an association between antioxidant intake and pulmonary function. Because there are fewer studies that evaluated COPD as a specific end point, there is limited/suggestive evidence of an association between diet and COPD. Nonetheless, it is premature to recommend specific dietary interventions for COPD prevention until further data are available. Randomized supplementation studies have shown increased risks of cancer and mortality, raising important safety concerns about high-dose vitamin supplementation.

**Tuberculosis and the Risk of COPD**

Pulmonary tuberculosis can lead to scarring and accelerated decline in lung function (283). In the PLATINO (Proyecto Latinoamericano de Investigación en Obstrucción Pulmonar) study (284) and PREPOCOL (Prevalencia de EPOC en Colombia) study (205), which are population-based surveys to estimate the prevalence of COPD using spirometry, a report of previous tuberculosis or previous treatment for tuberculosis was strongly associated with a greater risk of COPD as defined by the GOLD criteria. For instance, the PLATINO study, which was performed in five large cities in Latin America, found a smoking-adjusted odds ratio of 2.3 (95% CI, 1.5–3.6). The PREPOCOL study, which included five Colombian cities, found an adjusted odds ratio of 4.8 (95% CI, 4.0–5.9). Smoking (285) and exposure to biomass smoke (286, 287) have been associated with an increased risk of tuberculosis, demonstrating the complex interactions between inhalation of smoke and altered lung function. In countries with a high burden of tuberculosis, it may contribute substantially to the prevalence of irreversible airflow obstruction.

**Tuberculosis and COPD: conclusions.** There is limited/suggestive evidence of an association between tuberculosis and chronic airflow obstruction. There remains uncertainty, however, about whether tuberculosis-related irreversible loss of lung function is clinically similar to COPD from other causes, such as personal cigarette smoking. Therefore, the evidence is inadequate to infer the presence or absence of a causal relationship between tuberculosis and COPD.

**OVERALL CONCLUSION**

Cigarette smoking is the most important single risk factor for the development of COPD. A substantive burden of disease, however, occurs in the absence of smoking, especially among younger persons, women, and residents of developing countries and the PAF for smoking is generally less than 80%. On the basis of our review, there are important novel risk factors for COPD. Strong
evidence implicates genetic syndromes, such as α1-antitrypsin deficiency, and occupational exposures as causes of COPD. Outdoor air pollution from traffic and other sources, secondhand smoke, biomass smoke, and dietary factors are likely causes of COPD, although the evidence is not sufficiently conclusive to infer a causal relationship. Chronic asthma and tuberculosis are likely causes of lung function decrement and can, as such, result in irreversible airway obstruction. It remains unclear, however, whether the clinical features and natural history of these conditions, when accompanied by irreversible airway obstruction, are the same as COPD as a specific disease entity.

Further research is needed to confirm the causal effect of outdoor air pollution, secondhand smoke, biomass smoke, diet, tuberculosis, and chronic asthma on the development of COPD. Prospective epidemiological studies with adequate numbers of nonsmokers and careful control for other confounding variables will be required. In some cases, such as for biomass smoke exposure, clinical trials of exposure reduction would provide strong evidence about its role in COPD causation. Further research on genetic polymorphisms is needed to uncover more subtle risk factors for COPD and gene–environment interactions. Studies reviewed in this document indicate that nontraditional risk factors, such as outdoor air pollution exposure and asthma, may negatively affect the growth of lung function early in life. Additional longitudinal research is needed to determine whether the impact of these risk factors on the growth, plateau, or decline in lung function ultimately translates into a greater risk of COPD as defined by GOLD or other objective clinical categorizations.

In public health terms, exposure to these less traditional risk factors likely contributes substantively to the increasing global burden of COPD. Especially in the developing world, where smoking prevalence is low and biomass is commonly burned for fuel, the majority of COPD cases may not be explained by smoking. Moreover, the interaction of smoking and other exposures, particularly occupational exposures, may greatly increase the risk of COPD. Consequently, public efforts to prevent COPD must target both smoking cessation and the reduction of these other exposures. Addressing one without the other will not effectively ameliorate the population burden of COPD.

This statement was prepared by an ad hoc subcommittee of the ATS Environmental and Occupational Health Assembly.

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