American Thoracic Society Documents

An Official American Thoracic Society Public Policy Statement: Novel Risk Factors and the Global Burden of Chronic Obstructive Pulmonary Disease

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THIS OFFICIAL STATEMENT OF THE AMERICAN THORACIC SOCIETY (ATS) WAS APPROVED BY THE ATS BOARD OF DIRECTORS, MARCH 2010

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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 nonsmoking 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 α_1-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.

This document has an online supplement, which is accessible from this issue's table of contents at www.atsjournals.org

Am J Respir Crit Care Med Vol 182. pp 693–718, 2010
DOI: 10.1164/rccm.200811-1757ST
Internet address: www.atsjournals.org

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 Long 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-

ified Bradford Hill criteria"; *see* Appendix E1) (6, 7). Careful consideration of the role of chance, bias, and confounding was also applied to the evaluation of each study cited in this report.

The hierarchy for classifying the strength of causal inferences was derived from that used by the U.S. Surgeon General. The suggestive/nonsufficient category is expanded and operationalized according to the approach used by the Institute of Medicine (*see* Appendix E1) (8).

We developed Forest plots for two risk factor areas, secondhand smoke and biomass, in which most studies reported odds ratios. Meta-analysis was used to generate summary odds ratios, using a random effects model. Stata 10 (StataCorp, College Station, TX) was used ("metan" module).

Growth, Plateau, and Decline of Pulmonary Function: 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_1), 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_1), 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_1 have relevance for COPD causation, even if these studies did not evaluate COPD as a specific study outcome.

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

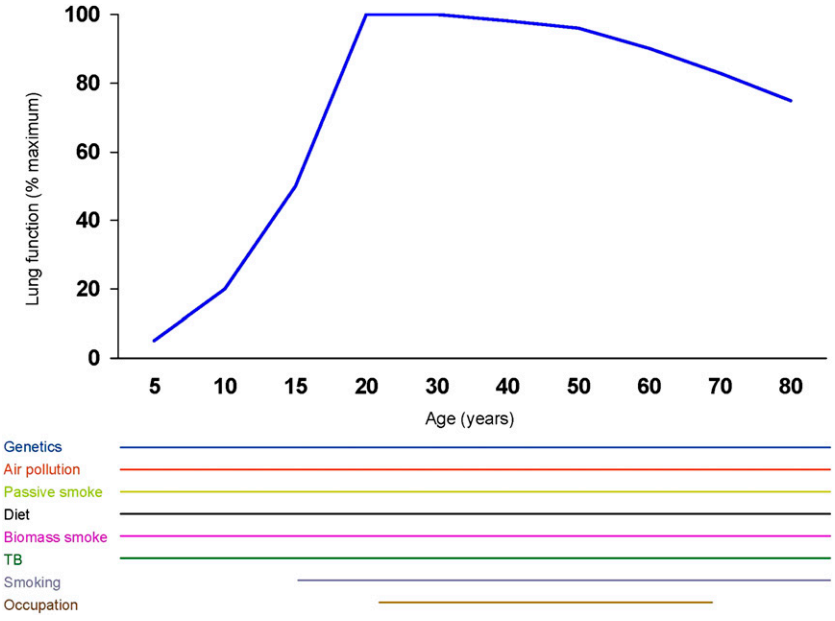

Figure 1. Theoretical model of how exposures affect pulmonary function throughout the life span. Shown is the idealized growth, plateau, and decline of lung function, based on the work of Speizer and Tager (Epidemiology of chronic mucus hypersecretion and obstructive airways disease. *Epidemiol Rev* 1979;1:124–142). The *horizontal bars* at the *bottom* show the time period during which each exposure is presumed to affect pulmonary function during the life span. For example, passive smoke exposure may decrease the growth and plateau phase of lung function development and accelerate the decline of lung function, whereas occupational exposures and direct personal smoking begin later in life.

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

Study (Ref.)	Follow-up Period	Population	Sample Size	Smoking Status	Outcome Measurement	Adjusted OR (95% CI)	Population-attributable Fraction (%)
Lindberg *et al.*, 2005; Sweden (35)	Cohort, 10-yr follow-up	Population-based sample, 46–77 yr	1,109	Persistent smokers, 24.1% Persistent ex-smokers, 26.3% Quitters, 12.0% Restarters, 2.0% Persistent nonsmokers, 34.1%	BTS: FEV_1/FVC <0.7 and FEV_1 < 80% GOLD: FEV_1/FVC <0.7	BTS Persistent smokers, 5.37 (2.82–10.26) Persistent ex-smokers, 1.01 (0.46–2.17) Quitters, 2.32 (1.02–5.3) Restarters, 3.13 (0.65–15.9) GOLD Persistent smokers, 4.56 (2.67–7.79) Persistent ex-smokers, 1.03 (0.58–1.83) Quitters, 1.34 (0.63–2.86) Restarters, 3.57 (1.06–12.00)	BTS: 48.3 GOLD: 48.6
Lindberg *et al.*, 2006; Sweden (19)	Cohort, 7-yr follow-up	Population-based sample, 46–77 yr	963	Smokers, 24% Ex-smokers, 35% Nonsmokers, 41%	FEV_1/FVC <0.7, FEV_1 <80%	Ex-smokers, 4.01 (1.52–10.55) Smokers, 9.92 (3.82–25.82)	76.2
Lokke *et al.*, 2006; Denmark (21)	Cohort, 25-yr follow-up	Population-based sample	8,045	Continuous smokers, 30.4% Ex-smokers, 18.3% Early cessation, 4.6% Intermediate cessation, 7.6% Late cessation, 10.4% Nonsmokers, 28.7%	FEV_1/FVC <70%, FEV_1 <80%	Continuous smokers, 6.3 (4.2–9.5) Ex-smokers, 1.1 Early cessation, 1.8 Intermediate cessation, 2.8 Late cessation, 4.7	74.6
de Marco *et al.*, 2007; Europe (14)	Cohort; median follow-up, 8.9 yr	Random population sample, 20–44 yr	5,002	Ever-smokers (<15 pack-years), 37.6% Ever-smokers (>15 pack-years), 18.0% Nonsmokers, 44.4%	FEV_1/FVC <70%, doctor-diagnosed asthma excluded	Ever-smokers (<5 pack-years), 1.42 (1.02–1.98) Ever-smokers (⩾15 pack-years), 3.76 (2.76–5.12)	39.6

Definition of abbreviations: BTS = British Thoracic Society; CI = confidence interval; GOLD = Global Initiative for Chronic Obstructive Long Disease; OR = odds ratio.

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 FEV_1, 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 FEV_1. In one of the few studies of nonsmokers exclusively, there was evidence of significant familial aggregation of both FEV_1 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 [$FEF_{25–75}$] and $FEF_{25–75}/FVC$) 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.

TABLE 2. FAMILIAL AGGREGATION OF PULMONARY FUNCTION IN NONSMOKERS

Study (Ref.)	Type of Study	Population	Sample Size	Respiratory Outcome Measurement	Findings*	Study Limitations
Man, 1976 (38)	Twin	Asymptomatic nonsmoking same-sex twin pairs between ages 18 and 48 yr	10 pairs of monozygotic twins and 6 pairs of dizygotic twins	Lung volumes and maximal expiratory flow–volume curves	Smaller intrapair differences for MZ than DZ twins for vital capacity and maximal flow rate at 60% of TLC	Small sample size No adjustment for height
Hubert, 1982 (40)	Twin	Middle-aged males from NHLBI Twin Study	127 pairs of monozygotic twins and 141 pairs of dizygotic twins; only 148 subjects were nonsmokers	FEV_1 and FVC	Significant heritability for FEV_1 (0.74) after adjustment for age, height, weight, and pack-years Significant heritability for FVC not shown	Most study participants were smokers
Redline, 1987 (41)	Twin	Same-sex adult twins in the Greater Boston Twin Registry	256 monozygotic and 158 dizygotic twin pairs; only 163 individuals were nonsmokers	FEV_1 and FVC	Significant intrapair correlations for both FEV_1 and FVC among MZ twins, with magnitude of correlations approximately twice as great in MZ vs. DZ pairs	Most study participants were smokers
Ghio, 1989 (39)	Twin	Same-sex twin pairs who were asymptomatic university students and nonsmokers	74 pairs of asymptomatic, nonsmoking twins (47 MZ, 27 DZ)	FEV_1, FVC, $FEF_{25–75}$, lung volumes, and $D_{L_{CO}}$	No conclusive evidence of significant heritability of any phenotype studied after height adjustment, although $FEF_{25–75}$ was borderline	Small sample size Young age of subjects (mean, 20 yr)
Higgins, 1975 (288)	Family	Residents of Tecumseh, MI	9,226 subjects, general population	FEV_1	Significant correlations between FEV_1 of parents and children under age 40 yr Significant correlations for FEV_1 values of same-sex siblings at all ages	Smokers were included, but no adjustment for smoking No separate analysis of nonsmokers
Tager, 1976 (289)	Family	Households from East Boston, MA	469 individuals from 148 households	FEV_1	Significant correlations between mid-parental FEV_1 and child's FEV_1 Significant correlations between siblings' FEV_1 No significant correlations between spouses' FEV_1	Smokers were included, but no adjustment for smoking No separate analysis of nonsmokers
Lewitter, 1984 (290)	Family	Families from East Boston, MA	1,358 individuals from 404 nuclear families	FEV_1 and $FEF_{25–75}$	Path analysis demonstrated: Significant heritability for FEV_1 (0.45) Significant heritability for $FEF_{25–75}$ (0.45)	Smokers were included, with adjustment for smoking status No separate analysis of nonsmokers
Devor, 1984 (42)	Family	Mennonite families in Kansas	307 asymptomatic nonsmokers in nuclear families	FEV_1 and FVC	Path analysis using the XTAU model demonstrated: Significant transmissible variation for both FEV_1 (0.17) and FVC (0.20) Significant effects of shared sibling environment on sibling correlations	Unable to separate cultural from genetic influences
Lebowitz, 1984 (291)	Family	Nuclear families from the Tucson Epidemiology Study of Airway Obstructive Diseases	899 individuals in nuclear families	FEV_1, FVC, $Vmax_{50}$, and $Vmax_{75}$	Significant correlations for parent–child FEV_1 and FVC without covariate adjustment After adjustment for ponderal index, no significant familial correlations were noted	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
Astemborski, 1985 (292)	Family	Families ascertained through control subjects in Baltimore	439 adults from 108 nuclear families	FEV_1 and FEV_1/FVC	Variance component analysis demonstrated: Additive genetic factors accounted for 28% of variation in FEV_1 Additive genetic factors accounted for 24% of variation in FEV_1/FVC	Smokers were included, with adjustment for smoking status No separate analysis of nonsmokers

(*Continued*)

TABLE 2. (CONTINUED)

Study (Ref.)	Type of Study	Population	Sample Size	Respiratory Outcome Measurement	Findings*	Study Limitations
Silverman, 1998 (43)	Family	Extended pedigrees of severe early-onset COPD probands and control probands	204 first-degree relatives of COPD probands and 83 control family members	FEV_1, FEV_1/FVC, FEV_1<80% pred, and FEV_1 <60% pred	Reduced FEV_1 and FEV_1/FVC and increased risk of FEV_1 < 60% and FEV_1 <80% found in smoking first-degree relatives of subjects with COPD compared with smoking control subjects No increased risk for reduced FEV_1 or FEV_1/FVC in nonsmoking relatives of COPD probands compared with nonsmoking control subjects	Small sample size for control subjects
Palmer, 2001 (293)	Family	Nuclear families from Busselton in Western Australia	1,874 individuals from 468 nuclear families, using spirometry when subject was an adult	FEV_1 and FVC	Heritability estimates of 0.39 for FEV_1 and 0.41 for FVC	Smokers were included, with adjustment for smoking status No separate analysis of nonsmokers
McCloskey, 2001 (44)	Family	Nuclear families of COPD case subjects in the UK	173 siblings of COPD case subjects and 419 population-based control subjects	FEV_1 and FEV_1/FVC	Current or ex-smoking siblings of COPD probands had odds ratio of 4.7 for COPD (FEV_1 <80% pred and FEV_1/FVC < 0.7) compared with control smokers All of the nonsmoking sibling of COPD probands had normal spirometry	Small sample of nonsmoking siblings
DeMeo, 2004 (45)	Family	Extended pedigrees of severe, early-onset COPD probands and control probands	333 first-degree relatives of COPD probands and 83 control family members	FEF_{25-75} and FEF_{25-75}/FVC	Significantly lower FEF_{25-75} and FEF_{25-75}/FVC in smoking first-degree relatives of COPD probands compared with smoking control subjects Significantly lower FEF_{25-75} and FEF_{25-75}/FVC in nonsmoking relatives of COPD probands compared with nonsmoking control subjects	Small sample size for control subjects

Definition of abbreviations: % pred = percentage of predicted value; COPD = chronic obstructive pulmonary disease; D_{LCO} = diffusing capacity of the lung for carbon monoxide; DZ = dizygotic twins; FEF_{25-75} = forced expiratory flow, mid-expiratory phase; MZ = monozygotic twins; $Vmax_{50}$ = maximal expiratory flow rate at 50% of vital capacity; $Vmax_{75}$ = 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 FEV_1/VC on chromosome 14; they also found several other genomic regions with possible linkage to phenotypes defined by spirometry.

Severe α_1-antitrypsin deficiency in nonsmokers. Severe α_1-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 some nonsmokers, but significant associations have not typically been reported for nonsmokers (67). A study using data from the Framingham Heart Study focused on a positional candidate gene, *SMOC2*, located within a region of linkage to FEV_1 on chromosome 6

TABLE 3. CROSS-SECTIONAL STUDIES DEMONSTRATING IRREVERSIBLE AIRWAY OBSTRUCTION IN CLINICAL SAMPLES OF ADULTS WITH ASTHMA

Study (Ref.)	Population	Proportion of Smokers	Prednisone Reversal	Lung Function Outcome Measurement	Outcome	Risk
Brown, 1984 (69)	89 consecutive patients	43%	Yes	FEV_1 <70% predicted	19%	Age, duration, severity
ten Brinke, 2001 (75)	136 patients with severe disease	30% (<10 pack-years)	No*	FEV_1/FVC < 75% predicted	49%	Age, duration, sputum eosinophils
Ulrik, 1999 (70)	92 patients	None	No	FEV_1 <80% predicted	23%	Large initial dilator response
Vonk, 2003 (76)	228 patients	30% patients with asthma	No	Irreversibility	16%	Severity: low initial FEV_1, reactivity, reversibility
Cassino, 2000 (71)	75 patients >60 yr	None	No	Mean FEV_1 (% predicted)	Long duration = 60% vs. short duration = 80%	Duration, not severity
Bumbacea, 2004 (74)	66 patients with severe disease	30%	No*	Mean FEV_1 (% predicted); compare reversible with irreversible	Nonreversible = 50% vs. reversible = 80% predicted	Age, duration Blood eosinophils Bronchial disease on HRCT
Hudon, 1997 (77)	36 patients (18 reversible, 18 nonreversible), age and sex matched	14% (<7 pack-years)	Yes	Mean FEV_1 (% predicted); compare reversible with irreversible	Nonreversible = 49% vs. reversible = 80%	Duration Bronchial disease on HRCT

Definition of abbreviation: HRCT = high-resolution computed tomography.
* Clinical improvement after treatment with prednisone.

(68). In nonsmokers, these investigators found significant associations between several single-nucleotide polymorphisms in *SMOC2* with FEV_1 and FVC.

Genetic risk factors for COPD: conclusions. There is limited/suggestive evidence of familial aggregation of pulmonary function among nonsmokers. α_1-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 FEV_1) 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 FEV_1 (20 ml/yr) is a normal feature in healthy nonsmoking subjects (84, 85). Several studies revealed an excess decline in FEV_1 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 FEV_1 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 FEV_1 among persons with asthma appear to be as follows: low baseline lung function (FEV_1% predicted) (87, 92, 95), less reversibility to β_2-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 FEV_1 in adulthood (104–106). There is evidence of an exposure–response gradient, with greater childhood asthma severity relating to poorer adult FEV_1. In the Tucson study, persistent wheezing between ages 3 and 6 years, which is associated with an asthmatic phenotype, was associated with lower FEV_1 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 FEV_1 in adulthood are as follows: low baseline FEV_1

(97, 108–111), more severe bronchial hyperresponsiveness (97, 99), early onset of respiratory symptoms (112), more severe respiratory symptoms (111, 112), persistent wheezing (113, 114), female sex (115), and smoking (112).

Asthma and the development of 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 FEV_1.

Several longitudinal studies in children are now available (Table E5). 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 (NO_2), 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 (PM_{10}), measured within 8 km of personal residences, was negatively associated with FVC, FEV_1, and FEV_1/FVC. Higher PM_{10} was also related to an increased risk for COPD (odds ratio [OR], 1.33 per 7 $\mu g/m^3$; 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 PM_{10} declined over this time period. An 11-year reduction of PM_{10} by 10 $\mu g/m^3$ was associated with a decreased rate of annual decline of lung function corresponding to 9% (FEV_1), 6% (FEV_1/FVC ratio), and 16% ($FEF_{25–75}$). 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 PM_{10} was related to an increased risk for COPD (OR, 1.33 per 7 $\mu g/m^3$; 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 NO_2 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

Study (Ref.)	Type of Study	Population and Age Group	Sample Size	Exposure Measurement	Respiratory Outcome Measurement	Adjusted Association, Slope, or Odds Ratio (95% CI or *P* Value)	Other Findings	Study Limitations
Longitudinal Studies of Children								
Avol, 2001 (133)	Cohort with "intervention" (due to moving); 5-yr follow-up	"Movers" of two cohorts (enrolled in 1993 at age 10 yr or in 1994 at age 11 yr; follow-up to age 15 yr)	59 boys, 51 girls	Difference in urban background pollution (PM_{10}, NO_2, O_3) at pre- and postmoving residence	Annual growth in FEV_1 (ml), MMEF (ml/s), PEF (ml/s)	Per 10-$\mu g/m^3$ increase in PM_{10}: FEV_1: −6.6 (−13.5 to 0.3) MMEF: −16.6 (−32.1 to −1.1)	Interpretation: Children moving to cleaner air improved lung function growth; ("to move" can be considered an "exposure intervention") Similar findings for peak flow	Sample size
Gauderman, 2000 (131)	Prospective cohort (three age groups); 4-yr follow-up	4th, 7th, and 10th graders recruited in 1993 from schools selected from 12 communities	1,498 4th graders; 802 7th graders; 735 10th graders	Urban background air pollution (central monitors for PM_{10}, $PM_{2.5}$, NO_2, O_3, inorganic acid)	Annual lung function growth rate (average PFT measurements per child: 3.8)	Annual FEV_1 growth deficit, 4th grade cohort: PM_{10} (per 51.5-$\mu g/m^3$ annual mean): −0.85% (−1.59 to −0.10%) Predicted 4-yr growth deficit in most polluted area: −3.4%	Similar results for other markers of pollution (e.g., NO_2), asthmatics and nonasthmatics. Similar findings in 7th and 10th graders but not significant	No data on local traffic-related exposures
Gauderman, 2002 (130)	Prospective cohort (one age group); 4-yr follow-up	4th graders recruited in 1996 from schools selected from 12 communities (mean age, 9.9 yr)	1,678 with at least 2 PFTs, 1996 to 2000	Urban background air pollution (central monitors for PM_{10}, $PM_{2.5}$, NO_2, O_3, inorganic acid, elemental carbon)	Annual lung function growth rate (average PFT measurements per child: 3.8)	All estimates were negative; several reached statistical significance. Annual growth deficits per 22.2 $\mu g/m^3$ $PM_{2.5}$: FEV_1: −0.39% (−1.06 to 0.28%) MMEF: −0.94% (−1.87 to 0.0%)	Stronger effects in those more outdoors Largely confirms Gauderman, 2000 (131) 4th grade results	No data on local traffic-related exposures
Gauderman, 2004 (129)	Prospective cohort (one age group); 8-yr follow-up	4th graders recruited in 1993 (same as Gauderman, 2000 [131])	n = 1,759 with repeated PFT; n = 747 with tests in 1993 and 2001	Urban background air pollution (central monitors for PM_{10}, $PM_{2.5}$, NO_2, O_3, inorganic acid, elemental carbon)	8-yr growth deficit of FVC (ml), FEV_1 (ml), MMEF (ml/s)	8-yr deficit per 22.8 $\mu g/m^3$ $PM_{2.5}$: FEV_1:-79.7 ml (−153.0 to −6.4) MMEF: −168.9 (−345.5 to 7.8)	Estimates for all urban pollutants negative (FVC, FEV_1, MMEF); mostly statistically significant for FEV_1 and MMEF Similar for the 747 with complete follow-up In most polluted area: FEV_1 < 80% at age 18; 7.9% in most polluted area (1.6% in least)	No data on local traffic-related exposures Relationship to future COPD?
Gauderman, 2007 (132)	Prospective cohort (one age group); 8-yr follow-up)	School-based sample from 12 communities; 9–11 yr; 8-yr annual follow-up (1993–2000)	22,686 lung function tests from 3,677 children	Distance: <500 m from local freeway Regional pollutants (acid, NO_2, PM_{10}, $PM_{2.5}$)	8-yr growth of FEV_1 (and other lung function measures)	Living < 500 m of freeway vs. <1,500 m: Growth: FEV_1: −81 ml (−143 to −18 ml) Deficit at age 18: FEV_1: 97% predicted (94.6–99.4)	Regional pollutants independently associated with FEV_1 growth (confirms Gauderman, 2004 [129]) Similar findings for small airway function For "distance to main roads" no significant results	Not yet clear how "freeway distance" and distance to major roads interact in determining levels of relevant pollutants

(*Continued*)

TABLE 4. (CONTINUED)

Study (Ref.)	Type of Study	Population and Age Group	Sample Size	Exposure Measurement	Respiratory Outcome Measurement	Adjusted Association, Slope, or Odds Ratio (95% CI or *P* Value)	Other Findings	Study Limitations
Horak, 2002 (136)	Prospective cohort; 3-yr follow-up	2nd and 3rd graders from 8 towns (age, 6–9); 1994–1997	n = 975 recruited; n = 860 with follow-up; PFT 2× per yr	Central monitoring data for PM_{10}, NO_2, O_3, SO_2, stratified by summer/winter mean	Annual lung function growth deficit per 10 $\mu g/m^3$ PM_{10}	FEV_1: −84 ml/yr ($P = 0.003$) MMEF: −329 ml/s/yr ($P < 0.001$)	Winter PM_{10} also significantly associated with FEV_1 growth	Short follow-up; seasonal analyses; partly inconsistent with findings from same cohort with 1 yr fewer data (Frischer *et al.*, 1999 [138])
Rojas-Martinez, 2007 (134)	Prospective cohort; 3-yr follow-up	Children (age 8 yr) from 39 randomly selected schools near to monitors; 1996–1999	n = 3,170 enrollees; PFT 2× per yr	Central monitor data close to school: PM_{10}, NO_2, O_3	Annual lung function growth, per IQR of pollutant	Annual growth per 36.4 $\mu g/m^3$ PM_{10}: Girls: FEV_1: −29 ml (−36 to −21) FEF_{25-75}: −17 ml/s (−36 to 1) Boys: FEV_1: −27 ml (−34 to −19) FEF_{25-75}: −18 ml/s (−34 to −2)	PM_{10}, NO_2, and O_3: associated (mostly significant) with growth deficits of FVC, FEV_1, and FEF_{25-75}, in boys and girls. Effect on FVC stronger, thus FEV_1/FVC positively associated with pollution	Relatively short follow-up; no local traffic-related pollution measurements
Holguin, 2007 (124)	Panel study, analyzed by cross-sectional analysis of lung function data (4-mo repeated measurements)	6–12 yr; school-based sample (asthmatic and nonasthmatic)	n = 194 (95 asthmatic, 99 nonasthmatic)	GIS model for NO_2 and EC at school; school road density; home road density	IQR increase in road density within 50-, 100-, 200-m buffer	FEV_1 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)	Exhaled NO also associated with traffic	Findings restricted to asthmatics; no associations in nonasthmatics Small sample Analysis of panel data was cross-sectional
Gotschi, 2008 (294)	Prospective follow-up and cross-sectional analyses; ~10-yr follow-up	Random population samples from 20 cities in 10 countries, age 20–44 yr at baseline (1991–1993); follow-up 2000–2002	4,290 with complete data	Annual mean from 1 single monitor per city ($PM_{2.5}$)	Level of lung function (FVC, FEV_1, FEV_1/FVC); annual change in lung function assessed in mixed models	Unadjusted model: negative associations with FEV_1 and FVC; adjusted models show no associations with $PM_{2.5}$ or other background pollutants	Strong correlation between city-level pollution and height and other covariates with north–south gradients	Local traffic-related exposure data among a small subsample suggest very large exposure misclassification in this cross-community analysis
Longitudinal Studies of Adults								
Sekine, 2004 (144)	Cohort; 8-yr follow-up (1987–1994)	Population sample of adult women age 30–59 yr, living >3 yr in same exposure area	Total: 733 women; n = 406 with PFT follow-up data	Distance to busy road, three groups: A: ≤20 m from busy road (47–56 ppb NO_2) B: 20–150 m (38–46 ppb NO_2) C: "behind roads" (24–36 ppb NO_2)	Adjusted change in FEV_1 for the three exposure groups	ΔFEV_1 per yr: A: −20 ml B: −15 ml C: −9 ml *P* for trend < 0.001 translates roughly to a −5 ml faster decline per yr per 11 ppb NO_2	Similar trend for FVC but not statistically significant	Only three comparison areas; those were, however, selected on the basis of traffic-related pollution
Downs, 2007 (141)	Cohort; 11-yr follow-up	Population sample of adults from 8 cities; age 18–60 yr at baseline, 1991	n = 4,742 with follow-up data (2002)	11-yr change in individually assigned exposure, from validated dispersion model	Adjusted decline in lung function vs. change in pollution	Per 10 $\mu g/m^3$ reduction in PM_{10}, decline in FEV_1 reduced by 3 ml (0.03–6.2) (~9% of mean decline) Decline in FEV_1/FVC reduced by 0.06% (0.01–0.12)	Stronger effects in never-smokers	Not analyzed for GOLD-defined COPD

(*Continued*)

TABLE 4. (CONTINUED)

Study (Ref.)	Type of Study	Population and Age Group	Sample Size	Exposure Measurement	Respiratory Outcome Measurement	Adjusted Association, Slope, or Odds Ratio (95% CI or *P* Value)	Other Findings	Study Limitations
Karakatsani, 2003 (147)	Nested case–control	COPD case subjects selected within EPIC Greece (case series 1), verified by additional clinical assessment/lung function (case series 2)	168 case subjects and 168 matched control subjects (case series 2: subset of 84)	Past 5 yr and 20 yr assigned to residence (distance-weighted mean of closest NO_2 monitors)	COPD case	OR per one quartile of NO_2, recent 5 yr: Case series 1 (all): 1.18 (0.94–1.49) Case series 2: 1.37 (1.05–1.79)	Similar but attenuated findings for last 20 yr NO_2	No local traffic-related pollution data
Cross-sectional Studies of Adults: Objectively Defined COPD or FEV_1/FVC Ratio								
Schikowski, 2005 (139)	Consecutively recruited cross-sectional study	All women age 54–55 yr living in selected Rhine-Ruhr area, 1985–1994	4,757 women	Residential assignment of NO_2 and PM_{10} monitors, within 8-km grid; residential distance to major road with >10k cars/d	Lung function, including FEV_1/FVC and GOLD-defined COPD	COPD (FEV_1/FVC < 0.7) OR for <100 m of road: 1.79 (1.06–3.02) Mean difference per 16 $\mu g/m^3$ NO_2: 1.39 (1.20–1.63)	Similar findings for FEV_1 and FVC, respectively, and for reported cough	Women only
Kan, 2007 (142)	Cross-sectional analysis of ARIC (Atherosclerosis Risk in Communities) cohort	Lung function assessment 1987–1989 (ARIC visit 1); mean age: 54.2 (SD 5.8) yr	13,972 with geo-coded residence	Traffic density (quartiles); distance to major roads; per quartile	Lung function (FEV_1, FVC, FEV_1/FVC)	Deficit among quartile 4 (vs. 1): Women: FEV_1: −21.5 (−48.5 to −5.5); *P* for trend, 0.04 FVC: similar, but n.s. Living <150 m from major road	Traffic density in men: null findings in all models Distance (<100 m): age-adjusted model: negative trends in women and men; multivariate models: null findings	Potential overadjustment of associations (with adjustment for background pollution and neighborhood income)

Definition of abbreviations: COPD = chronic obstructive pulmonary disease; EC = elemental carbon; GIS = geographic information system; GOLD = Global Initiative for Chronic Obstructive Long 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_{10}, $PM_{2.5}$ = particulate matter of less than 10 and 2.5 μm, respectively.

Table 4 includes longitudinal studies of children, longitudinal studies of adults, and cross-sectional studies of adults that include the FEV_1/FVC ratio or objectively defined COPD. Only studies published since the review by Sunyer (119) are included.

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.

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

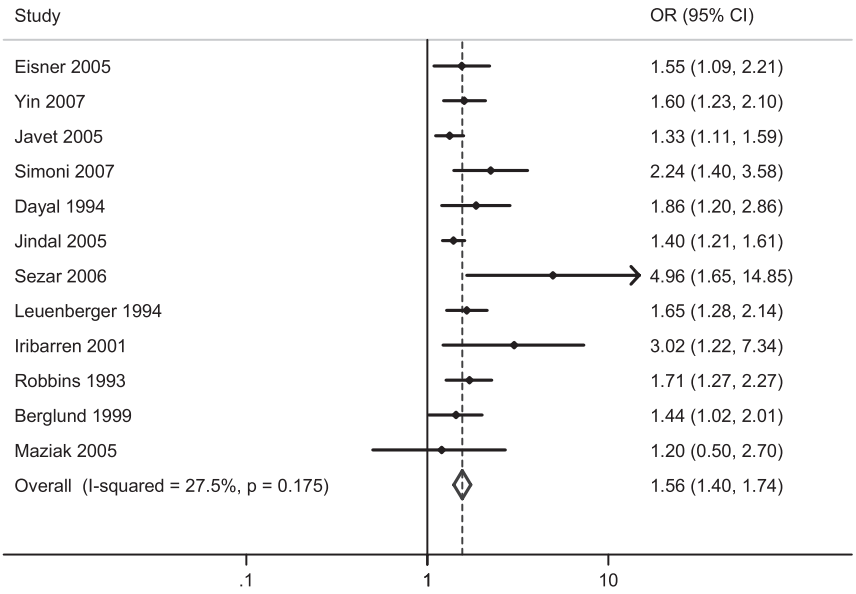

Figure 2. Secondhand smoke (SHS) exposure and the risk of COPD. Forest plot shows studies of SHS exposure and the risk of chronic obstructive pulmonary disease. Summary odds ratio was derived from meta-analysis with random effects model. CI = confidence interval; OR = odds ratio.

evidence of biological plausibility, in that exposure to air pollutants, such as particulate matter, O_3, and NO_2, can produce deleterious effects on the airway: airway oxidative stress, pulmonary and systemic inflammation, reduction in airway ciliary activity, amplification of viral infections, and increases in bronchial reactivity (148). 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 AHSMOG 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 reaching 10–30 mg/m^3 (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, 181–196). 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 measuring 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 stoves 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 FEV_1/FVC (191). In addition, an increase in the kitchen particulate concentration of 1,000 $\mu g/m^3$ was associated with a 2% reduction in FEV_1. 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 FEV_1/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

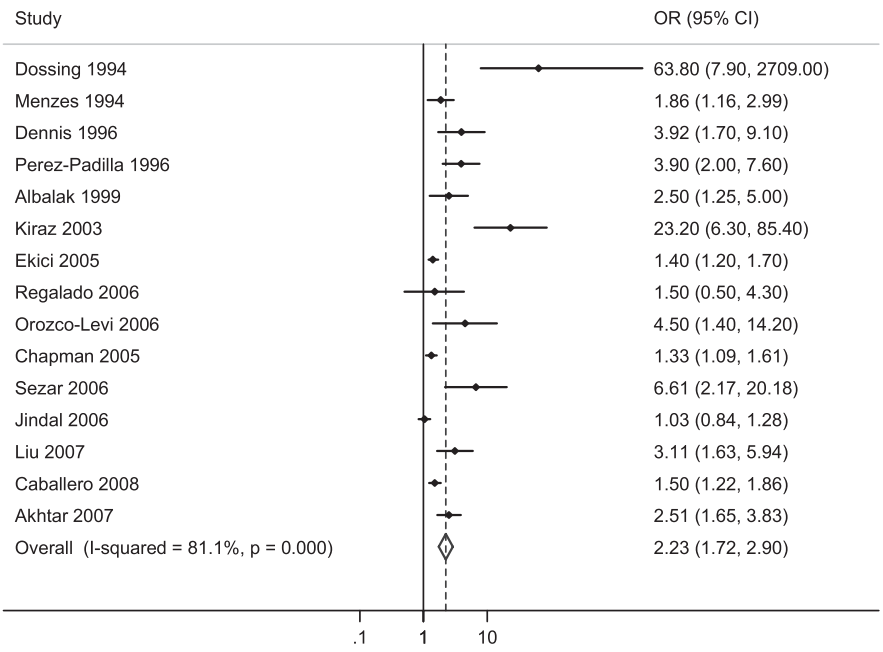

Figure 3. Biomass smoke exposure and the risk of chronic obstructive pulmonary disease (COPD). Forest plot shows studies of biomass smoke exposure and the risk of COPD. Summary odds ratio was derived from meta-analysis with random effects model. Exclusion of the two studies with largest variability (the Dossing and Kiraz studies) resulted in an odds ratio (OR) of 1.95 and a 95% confidence interval (CI) of 1.55–2.4.

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 FEV_1 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

Study (Ref.)	Type of Study	Population	Sample Size	Exposure Measure	Respiratory Outcome Measure	Adjusted Odds Ratio (95% CI or *P* Value)	Other Findings	Study Limitations
Korn *et al.*, 1987 (233)	Cross-sectional cohort	Population study of six cities in the United States	8,515 subjects	Self-report of occupational exposure to dusts, gases/fumes	$FEV_1/FVC < 60\%$	1.53 (1.17–2.08)	OR for chronic respiratory symptoms, 1.27–1.60	Potential exposure misclassification
Viegi *et al.*, 1991 (231)	Cross-sectional cohort	Population study of Po delta area in northern Italy	763 male subjects	Self-report of occupational exposure to dusts, gases, and fumes	$FEV_1/FVC < 70\%$	1.45	OR for chronic cough and phlegm, 1.69 and 1.64	Potential exposure misclassification
Fishwick *et al.*, 1997 (225)	Cross-sectional cohort	Population study of four areas in New Zealand (ECRHS)	1,132 subjects	Self-report of occupational exposure to dusts, gases, and fumes	$FEV_1/FVC < 75\%$ and chronic bronchitis symptoms	3.13 (1.07–9.12)	OR for bakers and spray painters, 25.5 and 14.4, respectively	Potential exposure misclassification
Sunyer *et al.*, 1998 (235)	Cross-sectional cohort	Population study of five areas in Spain (ECRHS)	1,735 subjects	Self-report of occupational exposure to dusts, gases/fumes; job–exposure matrix (high vs. low exposure)	$FEV_1/FVC < 70\%$	3.0 (1.0–9.4) for high mineral dust exposure	OR for cough >3 mo, 1.9 for high biological dust, 1.4 for high mineral dust; 1.7 for phlegm >3 mo for high gases/fumes	Potential exposure misclassification
Krzyzanowski *et al.*, 1986 (228)	Longitudinal cohort	Population study of Cracow, Poland	1,824 subjects	Self-report of occupational exposure to dusts	Rate of decline in FEV_1	Accelerated decline in FEV_1 with exposure to dusts		Potential exposure misclassification
Humerfelt *et al.*, 1993 (226)	Longitudinal cohort	Population study of Bergen, Norway	951 subjects	Self-report of occupational exposures to 11 airborne agents (dusts, gases, vapors, and fumes)	Rate of decline in FEV_1	Accelerated decline in FEV_1 with exposure to sulfur dioxide gas and to metal fumes	Increased adjusted decline in FEV_1 in subjects exposed to increasing numbers of occupational agents (test for trend: $P < 0.01$)	Potential exposure misclassification
Bakke *et al.*, 1991 (224)	Cross-sectional cohort	Population study in Norway	1,512 subjects	Self-report of occupational exposures to 11 airborne agents (dusts, gases, vapors, and fumes)	Airflow limitation ($FEV_1/FVC < 0.70$ and $FEV_1 < 80\%$ of predicted)	Occupational exposures to quartz and asbestos dust were associated with airflow limitation	OR for obstructive lung disease (asthma or chronic obstructive lung disease), 3.6 (1.3–9.9) for high occupational exposure to airborne agents	Potential exposure misclassification
Xu *et al.*, 1992 (232)	Cross-sectional cohort	Population study in Beijing, China	3,606 subjects	Self-report of occupational exposure to dusts, gases/fumes	FEV_1, FEV_1/FVC, $FEF_{25–75}$	Dust exposure was associated with decreased FEV_1, FEV_1/FVC, and $FEF_{25–75}$; gas/fume exposure with decreased FEV_1 and FVC	OR for chronic respiratory symptoms, 1.30 (1.09–1.48) for dusts and 1.27 (1.09–1.48) for gases/fumes	Potential exposure misclassification
de Meers *et al.*, 2001 (247)	Cross-sectional cohort	Dutch population study (ECRHS)	1,906 subjects	Job–exposure matrix	FEV_1, FEV_1/FVC	Organic dust exposure was associated with decreased FEV_1, −63 ml (−118, −8); mineral dust exposure with decreased FEV_1/FVC, −1.1% (−1.8, −0.3)	OR for chronic bronchitis for mineral dust exposure, 2.22 (1.16-4.23)	Potential exposure misclassification

(*Continued*)

TABLE 5. (CONTINUED)

Study (Ref.)	Type of Study	Population	Sample Size	Exposure Measure	Respiratory Outcome Measure	Adjusted Odds Ratio (95% CI or *P* Value)	Other Findings	Study Limitations
Jaén *et al.*, 2006 (240)	Cross-sectional cohort	Population study of an urban-industrial area of Catalonia, Spain	497 subjects	Self-report of occupational exposure to dusts, gases, and fumes	FEV_1, FEV_1/FVC, $FEF_{25–75}$	>15-yr exposure to dusts, gases, or fumes associated with decreased FEV_1, −80 ml (−186, −26); FEV_1/FVC, −1.7% (−3.3, −0.2); $FEF_{25–75}$, −163 ml (−397, −71)		Potential exposure misclassification
Hnizdo *et al.*, 2002 (250)	Cross-sectional cohort	NHANES III population study in the USA	9,823 subjects	Self-report of longest job and standard coding of occupation and industry	COPD (FEV_1/FVC <0.70 and FEV_1 <80% of predicted)	ORs for COPD increased for multiple occupations and industries	Fraction of COPD attributable to work was estimated as 19.2% overall and 31.1% among never-smokers	Potential exposure misclassification
Matheson *et al.*, 2005 (243)	Cross-sectional cohort	Population study in Australia	1,232	Self-report of longest job and standard coding of occupation; job–exposure matrix	COPD (FEV_1/FVC <0.70 with either chronic sputum production or D_{LCO} <80% predicted and dyspnea)	2.70 (1.39–5.23) for biological dust exposure	OR for FEV_1/FVC <0.70 with chronic sputum production for gases and fumes exposure, 2.81 (1.01–7.79)	Potential exposure misclassification
Boggia *et al.*, 2008 (237)	Prospective cohort	Population-based work surveillance program in Italy	2,734 males	Self-report of vapor, dust, or fumes with expert review of job classification for confirmation	COPD (classic chronic bronchitis plus FEV_1/FVC <0.70 and FEV_1 <80% predicted)	Occupational exposure OR, 2.62 (2.02 to 3.41)	Combined effects of smoking and occupation found	Potential exposure misclassification; very conservative definition of COPD; males only
Weinmann *et al.*, 2008 (236)	Case control	Kaiser Permanente Northwest	388 COPD case subjects, 356 matched control subjects	Self-reported occupational exposure plus expert review	COPD diagnosis based on validated algorithm	Diesel exhaust, irritant gases and vapors, mineral dust, and metal dust most associated with COPD		Not all subjects had spirometry; potential exposure misclassification#
Blanc *et al.*, 2008 (238)	Case–control	Kaiser Permanente Northern California health plan members	1,202 adults with COPD, 302 matched control subjects	Self-reported VGDF on longest held job; job–exposure matrix	COPD (by health care use); subset with GOLD stage 2 or greater	VGDF: OR, 2.11 (1.59 to 2.82) Highest JEM category vs. lowest: OR, 2.27 (1.46 to 3.52)	Joint exposure to both smoking and VGDF markedly increased the risk of COPD (OR, 14.1; 95% CI, 9.33–21.2)	Younger patients with COPD (age, 45–65 yr); all health plan members

Definition of abbreviations: CI = confidence interval; COPD = chronic obstructive pulmonary disease; D_{LCO} = diffusing capacity of the lung for carbon monoxide; ECRHS = European Community Respiratory Health Survey; GOLD = Global Initiative for Chronic Obstructive Long Disease; JEM = job–exposure matrix; NHANES III = Third National Health and Nutrition Examination Survey; OR = odds ratio; VGDF = vapors, gas, dust, fumes.

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 α_1-antitrypsin (52, 265). Occupational exposure to dusts, gases, fumes, and/or smoke has been shown to increase risk of chronic cough, lower FEV_1, and lower FEV_1/FVC independent of personal tobacco use in these cohorts.

Occupation and COPD: conclusions. The evidence is sufficient to infer a causal relationship between occupational exposures and development of COPD. Consistent associations have been observed between exposure to workplace agents and COPD in multiple high-quality epidemiological studies. The association between occupational exposures and COPD is consistent and coherent when various definitions have been used (e.g.,

TABLE 6. ANTIOXIDANT NUTRIENT INTAKE, PULMONARY FUNCTION, AND RISK OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Reference	Type of Study	Population	Sample Size	Exposure Assessment	Respiratory Outcome	Other Findings	Study Limitation-comments
Vitamin E							
Schunemann *et al.*, 2002 (268)	Cross-sectional, USA, 1995–1998	Random sample from general population of northern USA	1,616 adults, 35–79 yr	6.9 mg/d	FEV_1, 1.29% increase from predicted value (0.16–2.41) FVC, NS	No effect of vitamin C after stratification by smoking: effect only in never-smokers FEV_1, 1.58% (0.008, 3.14) FVC, 1.96% (0.37, 3.55)	Adjusted for potential confounding variables including smoking and other antioxidants
Hu and Cassano, 2000 (295)	Cross-sectional	(NHANES III), USA, 1988–1994	18,162 adults, ⩾17 yr (NHANES III)	9.1 mg/d	FEV_1, 16.4 ml (5.5–27.4)	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	Serum levels positively related with FEV_1 effect observed among nonsmokers, former and current smokers
Butland *et al.*, 2000 (296)	Prospective cohort study with cross-sectional and longitudinal analysis	Sample of Welshmen aged 45–59 yr	2512 men, 45–59 yr	2.0 mg/d	FEV_1, 39 ml (95% CI, 6–69)		No significant effect of vitamin C, β-carotene, and magnesium intake
β-Carotene and Retinol							
Sharp *et al.*, 1994 (297)	Cross-sectional	Population-based part of ARIC cohort study	10,416 middle-aged adults	Dietary vitamin A, lowest vs. highest	FEV_1/FVC <65% OR, 1.1 (0.6–1.9)	Vitamin A protective in heavy current smokers in the upper tertile of cigarette smoke (>41 pack-years)	Adjusted for potential confounding variables including smoking
Grievink *et al.*, 1998 (298)	Cross-sectional; The Netherlands, 1994–1995		6,555 adults, 20–59 yr	2.5 mg/d	FEV_1, 66 ml (31.4–88.6) FVC, 75.5 ml (40.2–110.2)		Inconsistent results across studies
Hu and Cassano, 2000 (295)	Cross-sectional (NHANES III), USA 1988–1994	(NHANES III), USA, 1988–1994	18,162 adults ⩾17 yr	1.017 retinol equivalent (RE)	FEV_1, 18.2 (8.7–27.6)	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)	Serum levels positively related with FEV_1 effect observed among nonsmokers and former smokers
Chen *et al.*, 2001 (299)	Cross-sectional, Scottish	MONICA survey, 1995; random sample from general practitioner list	865 men and 971 women, 25 to 64 yr	100 μg/d	In men: FEV_1, NS FVC, 7.3 ml (SE, 3.1 ml) No significant effects in women		Adjusted for potential confounding variables including smoking and waist circumference
Other Carotenoids							
Schunemann *et al.*, 2002 (268)	Cross-sectional, USA, 1995–1998	Random sample from general population of northern USA	1,616 adults, 35–79 yr	1,825 μg/d lutein/xanthin	FVC, 1.7% increased from predicted value (0.8–2.6)	Interaction with smoking, greater effect in current smokers FEV_1, 2.54 (95% CI, 0.14, 4.94) FVC, 2.5% (95% CI, 0.53, 4.63)	Adjusted for potential confounding variables including smoking and other antioxidants

(*Continued*)

TABLE 6. (CONTINUED)

Reference	Type of Study	Population	Sample Size	Exposure Assessment	Respiratory Outcome	Other Findings	Study Limitation-comments
Flavonoids							
Tabak *et al.*, 2001 (300)	Cross-sectional	MORGEN Study, The Netherlands, 1994–1997	13,651 adults, 20–59 yr	117 vs. 15 mg/d	FEV_1, 44 ml higher (18–69) Lower chronic cough: OR, 0.80; 95% CI, 0.66–0.97		Adjusted for potential confounding factors including smoking
Omega-3 PUFAs							
Shahar *et al.*, 1994 (301)	Cross-sectional	Probability sampling in 4 U.S. communities, 1986–1989	8,960 current and former smokers	EPA and DHA	Inverse association with chronic bronchitis OR, 0.66 (0.52, 0.85) Emphysema OR, 0.31 (0.18, 0.52) COPD diagnosis (based on spirometry) OR, 0.50 (0.32, 0.79)		Adjusted for potential confounding factors including smoking
Tabak *et al.*, 1998 (302)	Ecological analysis of baseline information and 25-yr COPD mortality rate in 16 cohorts; baseline, 1959–1964	Seven Countries Study, 25-yr follow up	12,673 men, aged 40–59 yr	10% of mean baseline intake EPA and DHA: 0.1 g Fish: 4.4 g	25-yr COPD mortality EPA–DHA RR, 0.92 (0.84–0.99) Fish RR, 0.96 (0.92–1.00)	No significant effects of vitamin E, β-carotene, vitamin C, selenium, flavonoids, or n-6 fatty acids Protective effect of fruit intake	Potential misclassification of COPD Adjusted for potential confounding factors including smoking and occupation Heterogeneity of results within each cohort
McKeever *et al.*, 2008 (303)	Cross-sectional study	MORGEN–EPIC study, The Netherlands, 1994–1997	13,820 subjects (6,354 males and 7,466 females), aged 42 ± 11 yr	n-3 and n-6 fatty acid intake	FEV_1 No association with individual n-3 FA intakes Some n-6 FA were associated with lower FEV_1 ($C_{22:4}$, n-6 docosatetraenoic acid)	Interaction between n-6 FA and smoking on FEV_1	Adjusted for potential confounding factors including smoking and pack-years and vitamin C

Definition of abbreviations: ARIC = Atherosclerosis Risk in Communities; CI = confidence interval; COPD = chronic obstructive pulmonary disease; DHA = docosahexaenoic acid ($C_{22:6}$ [n-3]); EPA = eicosapentaenoic acid ($C_{20:5}$ [n-3]); FA = fatty acids; MONICA = Monitoring of Trends and Determinants in Cardiovascular Disease; MORGEN = Monitoring Project on Risk Factors and Health in the Netherlands; NHANES III = Third National Health and Nutrition Examination Survey; NS = not significant; OR = odds ratio; PUFAs = polyunsaturated fatty acids; RR = relative risk.

respiratory symptoms, fixed airway obstruction, physician diagnosis of COPD, and mortality from COPD). The temporal relationship has been established in prospective cohort studies. An exposure–response gradient was demonstrated in several studies. Biological plausibility is supported by data from experimental studies demonstrating the induction of chronic bronchitis and/or emphysema in animals after exposure to several agents associated with COPD in epidemiological studies.

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_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_1 during a 9-year period (267).

Other antioxidants, including vitamin E, carotenoids, and flavonoids, have also been evaluated. Greater FEV_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

(Table E8) (270, 271). 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 FEV_1 (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 FEV_1 over a 7-year time period (274). Notably, a decrease in consumption was associated with a decline in FEV_1. 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 FEV_1 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 FEV_1 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 nitrites 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 FEV_1 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 α_1-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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Author Disclosure: M.D.E. became an employee of Genentech subsequent to submission of manuscript; he was a consultant to Genentech ($5,001–$10,000) and Novartis ($5,001–$10,000), was an expert witness for DLA Piper LLP ($5,001–$10,000), received research grants from Roche ($50,001–$100,000) and NIH (more than $100,001), and an NIH study section reviewer (up to $1,000). N.A. served on an advisory board of GlaxoSmithKline ($5,001–$10,000) and as chair of the American Lung Association asthma clinical centers research project ($15,000/year). D.C. served on advisory boards of Boehringer Ingelheim (up tp $1,000) and Pfizer (up to $1,000) and as a grant reviewer for the State of California Tobacco-Related Disease Research Program (up to $1,000) and the Flight Attendant Medical Research Institute (up to $1,000). N.K. holds stock in Roche Holding Basel ($1,001–$5,000). R.P-P. received lecture fees from GlaxoSmithKline (up to $1,000) and Boehringer Ingelheim (up to $1,000). D.P. served on advisory boards of GlaxoSmithKline (up to $1,000), AstraZeneca (up to $1,000) and Nycomed (up to $1,000); he received lecture fees from GlaxoSmithKline ($1,001–$5,000), AstraZeneca ($1,001–5,000), and Nycomed ($1,001–$5,000), and received research grants from GlaxoSmithKline (more than $100,001), AstraZeneca ($50,001–100,000) and Nycomed ($50,001–100,000). I.R. reported she had nothing to disclose relevant to this manuscript. E.K.S. was a consultant to GlaxoSmithKline ($10,001–$50,000) and AstraZeneca ($5,001–$10,000), received lecture fees from GlaxoSmithKline ($1,001–$5,000), AstraZeneca ($1,001–$5,000) and Bayer ($1,001–$5,000), and research grants from GlaxoSmithKline (more than $100,001) and NIH (more than $100,001). J.R.B. served on an advisory board of the U.S. EPA ($1,001–$5,000), chaired the California Air Resources Board ($10,001–$50,000), and received book royalties from McGraw-Hill (up to $1,000).

Acknowledgment: The committee thanks Lance Lucas and Judy Corn of the American Thoracic Society for administrative support for this project.

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