American Thoracic Society Documents

An Official American Thoracic Society Statement: Work-Exacerbated Asthma

Paul K. Henneberger, Carrie A. Redlich, David B. Callahan, Philip Harber, Catherine Lemière, James Martin, Susan M. Tarlo, Olivier Vandenplas, and Kjell Torén, on behalf of the ATS Ad Hoc Committee on Work-Exacerbated Asthma

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***Rationale*: Occupational exposures can contribute to the exacerbation as well as the onset of asthma. However, work-exacerbated asthma (WEA) has received less attention than occupational asthma (OA) that is caused by work.**

***Objectives*: The purpose of this Statement is to summarize current knowledge about the descriptive epidemiology, clinical characteristics, and management and treatment of WEA; propose a case definition for WEA; and discuss needs for prevention and research.**

***Methods*: Information about WEA was identified primarily by systematic searches of the medical literature. Statements about prevention and research needs were reached by consensus.**

***Measurements and Main Results*: WEA is defined as the worsening of asthma due to conditions at work. WEA is common, with a median prevalence of 21.5% among adults with asthma. Different types of agents or conditions at work may exacerbate asthma. WEA cases with persistent work-related symptoms can have clinical characteristics (level of severity, medication needs) and adverse socioeconomic outcomes (unemployment, reduction in income) similar to those of OA cases. Compared with adults with asthma unrelated to work, WEA cases report more days with symptoms, seek more medical care, and have a lower quality of life. WEA should be considered in any patient with asthma that is getting worse or who has work-related symptoms. Management of WEA should focus on reducing work exposures and optimizing standard medical management, with a change in jobs only if these measures are not successful.**

***Conclusions*: WEA is a common and underrecognized adverse outcome resulting from conditions at work. Additional research is needed to improve the understanding of the risk factors for, and mechanisms and outcomes of, WEA, and to inform and evaluate preventive interventions.**

Keywords: asthma; occupational diseases; work-related asthma; exacerbation; work-exacerbated asthma

OVERVIEW

- Work-exacerbated asthma (WEA) is defined as pre-existing or concurrent asthma that is worsened by workplace conditions.
- Epidemiological studies conducted in general populations indicate that WEA occurs in a substantial proportion of adults with asthma, with a median prevalence estimate of 21.5%.
- A wide variety of conditions at work can exacerbate asthma symptoms, including irritant chemicals, dusts, second-hand smoke, common allergens that may be present at work, as well as other "exposures" such as emotional stress, worksite temperature, and physical exertion.
- Patients with WEA who experience persistent work-related symptoms resemble occupational asthma (OA) cases with respect to severity of asthma and medication requirements, as well as socioeconomic factors like unemployment and loss of labor-derived income.
- Compared with asthma unrelated to work, WEA is associated with more symptomatic days, a greater utilization of health-care resources, and a lower quality of life.
- The possibility of WEA should be carefully addressed in any working patient with asthma by inquiring about the work-relatedness of his/her asthma symptoms.
- There is limited evidence pertaining to the natural history of WEA. Avoidance or reduction of exposure can often lead to an improvement in asthma symptoms.

INTRODUCTION

Asthma is a prevalent chronic health condition, affecting approximately 7.7% of adults of working age (1). Exacerbation of asthma symptoms is common, with reports from recent surveys indicating that each year approximately half of individuals currently with asthma experience at least one episode of worsening of their asthma symptoms (1), 8.8% have an asthma-related emergency room visit (2), and 0.17% require hospitalization for asthma exacerbations (1). Preventing asthma exacerbations is important, since the occurrence of severe asthma exacerbations is associated with an accelerated decline of respiratory function (3).

The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the National Institute for Occupational Safety and Health.

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While exacerbation of asthma is often attributed to viral infections or failures in therapy, environmental conditions also make a substantial contribution. It is widely accepted that occupation is an important risk factor for asthma. A 2003 American Thoracic Society (ATS) Statement concluded that 15% of asthma among adults can be attributed to occupation (4). Also, the statement noted "that there may be much greater morbidity and productivity loss associated with exacerbations of pre-existing asthma due to workplace exposures" than from asthma caused by work (4). Although work-exacerbated asthma (WEA) is probably common, it has received much less systematic study than asthma that is caused by work (5).

The purpose of this statement is to critically review the medical literature on WEA to inform research and public health agendas. This Statement summarizes a comprehensive analysis of data pertaining to various aspects of WEA, focusing on the descriptive epidemiology. We conclude by discussing prevention and research needs.

METHODS

Methods used to develop this document are summarized in Table Ai in Appendix EA of the online supplement.

In July 2007, we used PubMed to implement a search of medical literature that combined the topics of asthma, occupation, and exacerbation. This yielded 1,150 references published during January 1, 1980, through June 30, 2007. Two researchers (K.T., P.K.H.) independently reviewed the 1,150 abstracts and identified articles likely to include findings on WEA. By this process, at least one of the two researchers selected 163 references, full-text articles were obtained for all but two of them, and the researchers examined the 161 articles to determine relevance to WEA. The same search strategy was implemented again to capture articles published between July 1, 2007, and August 28, 2009. One researcher (P.K.H.) reviewed the resulting 142 abstracts, determined that 22 were potentially relevant to WEA, and obtained and examined the 22 articles. The 183 full-text articles (i.e., 161 from 2007 and 22 from 2009) included 43 that were not relevant, 58 with helpful background information on work-related asthma (WRA), and 82 that addressed topics directly related to WEA: 51 frequency of WEA, 14 impact of WEA, 8 exposures, 8 diagnosis and detection, and 1 prevention. These articles were the core materials that informed this document. More details about this general search strategy and additional searches for specific topics are presented in Appendix EA.

Other information on WEA was sought from the reference lists in these articles, recent review books, documents published by the National Institute for Occupational Safety and Health, abstracts from recent ATS and European Respiratory Society conferences, and the American College of Chest Physicians (ACCP) consensus statement on the diagnosis and management of WRA (5). Members of the committee that developed the current document and those who reviewed it suggested other references.

The recommendations for prevention and for further research were proposed by individual committee members and discussed among the entire committee before inclusion in a draft version of this document. Committee members subsequently reviewed the draft document and suggested additional changes. Consensus was reached when no further changes in the recommendations were proposed.

DEFINING WORK-EXACERBATED ASTHMA

Work-related asthma subsumes two categories of disease: occupational asthma (OA) and WEA. Although the latter is the focus of this review, it is important to delineate the scope of the former in this context. OA refers to asthma caused by occupational exposures and can be due to sensitizers or irritants. Sensitizers are often subdivided into low-molecular-weight and high-molecular-weight agents. Irritant-induced OA includes reactive airways dysfunction syndrome (RADS), which results from a single high-dose exposure to irritants. WEA, unlike OA, is not initially brought about by occupational exposures, but rather is asthma that is worsened due to conditions at work.

The definitions proposed in the literature for asthma exacerbated by work vary according to whether they are used for epidemiological, clinical, or medico-legal purposes, similar to the definitions for asthma in the general asthma literature. Objective tests (e.g., serial measurements of the peak expiratory flow rate [PEFR] or FEV_1) to confirm suspected WEA have been more common in some clinic-based studies (6–11) than in epidemiologic studies. From surveillance conducted in the United States, only 5.2% of reported cases of work-related asthma had evidence in their medical records that pulmonary function testing had been conducted to confirm the relationship to work (12). Also, based on chart reviews for a group of work-related asthma cases in the Canadian province of Ontario, test results to support the work-relatedness of asthma were more common for OA cases (76%) than WEA cases (11%) (13). Clinicians and epidemiologists have often relied on self-reports to identify WEA cases, such as self-reports of doctor-diagnosed asthma and a work-related pattern of respiratory symptoms (worse at work or better away from work) or medication use (more on work days or less on nonwork days). Disease definitions tend to reflect medical practices and medico-legal considerations specific to their respective locales. For example, in Canada, specific inhalation challenge (SIC) testing is used in Quebec to distinguish OA from WEA cases among those with work-related asthma symptoms, but is not commonly used in other provinces.

Proposed WEA Case Definition

The term "work-exacerbated asthma" is used in this Statement to denote worsening of asthma due to conditions at work, regardless of frequency or duration of worsened asthma, and regardless whether there are permanent changes in asthma severity. For any individual, OA and WEA are not mutually exclusive, meaning that someone with OA can subsequently experience WEA, and vice versa.

The following case definition has four criteria and can be used in both clinical and research settings.

Criterion 1: Pre-existing or concurrent asthma. "Pre-existing asthma" is asthma with onset before entering the worksite of interest. The "worksite of interest" can be a new job or changes in exposures at an existing job due to the introduction of new processes or materials. "Concurrent asthma" or "coincident asthma" is asthma with onset while employed in the worksite of interest but not due to exposures in that worksite.

Criterion 2: Asthma–work temporal relationship. It is necessary to document that the exacerbation of asthma was temporally associated with work, based either on self reports of symptoms or medication use relative to work, or on more objective indicators like work-related patterns of serial PEFR.

Criterion 3: Conditions exist at work that can exacerbate asthma.

Criterion 4: Asthma caused by work (i.e., occupational asthma) is unlikely.

DESCRIPTIVE EPIDEMIOLOGY

Prevalence

Appendix EB contains summary descriptions of 55 studies that addressed the frequency of WEA. Characteristics and results of

the 12 studies that provided overall estimates of WEA prevalence are presented in Table 1. The 12 studies were conducted in general population or general health care settings in 7 countries. The definition of asthma was usually doctor-diagnosed asthma as determined from self-reports or medical records, although two studies also required evidence of bronchial hyperresponsiveness (BHR) (14, 15). All studies determined WEA status case by case, and most defined WEA based on self-reports of a relationship between work and asthma symptoms. Some of the studies in Table 1 reported prevalence as a percentage of all adults with asthma, and others as a percentage of all working adults with asthma. The latter type of prevalence was based on a more appropriate risk set for WEA, and was used preferentially for the two studies (16, 17) that reported both types of estimates. The prevalence of WEA from the 12 studies in Table 1 ranged from 13% to 58%, with a median of 21.5%.

Three of these studies used more objective criteria for WEA status (15, 17, 18). Caldeira and colleagues (15) reviewed information collected by interview to determine which individuals with pre-existing asthma had symptoms worsened by workplace exposures. The study by Bolen and others (18) used a work-related pattern of serial PEFR to define WEA. The more stringent criteria for WEA in the third study (17) required both self-reported work-related symptoms or medication use, and the judgment of an expert panel that there was exposure to asthma agents at work. These three studies with more objective criteria for WEA had prevalence estimates of 13% (15), 14% (18), and 22% (17), with a median of 14%.

Types of Jobs and Exposures Associated with WEA

Only a few studies have characterized exposures associated with WEA, and usually with broad categories for type of exposure or occupation. Jobs and exposures most closely associated with WEA are presented in Table 2. Surveillance data from the Sentinel Event Notification Systems for Occupational Risks (SENSOR) in the United States identified the occupation category of technical, sales, and administrative support, and the industry category of services as the most common among WEA cases (26). From the same study, the occupation category with the highest incidence rate for WEA was operators, fabricators, and laborers, with 5.8 WEA cases/10^5 working adults with asthma/year. The industry category with the highest rate was public administration, with 14.2 WEA cases/10^5 working adults with asthma/year (26). The occupations and industries associated with WEA often differed from those associated with OA (26). From a survey of adults with asthma, the types of industries associated with an elevated WEA prevalence were wholesale and retail trade, public administration, and transportation and public utilities (21).

Conditions at work that can exacerbate asthma are common. WEA is often associated with irritant exposures (6, 26, 27), and accidental exposures to high levels of chemicals can exacerbate pre-existing asthma (6). WEA has also been attributed to sensitizers such as common aeroallergens that are not specific to the work environment, and to other "exposures" such as emotional stress, worksite temperature, and physical exertion (6, 9, 12, 17, 25, 27). Also, several studies identified exposure to second-hand smoke as a cause of WEA (6, 14, 27, 28). Similar to differences in occupations and industries, the most common exposures are likely to differ for WEA compared with OA (6, 26).

Several impressions emerge from the studies presented in Table 2. First, many different workplace factors can contribute to the exacerbation of asthma. Second, exposure factors associated with exacerbation of asthma outside the workplace are also likely to be relevant within the workplace. Second-hand smoke is an example of such an exposure. Finally, there is a dearth of quantitative exposure data and information about what exposure levels might be safe for workers with asthma, but it appears likely that existing occupational health standards are inadequate to prevent WEA in many persons with asthma. In most instances, these standards were not designed to protect susceptible individuals such as those with asthma, and there is considerable heterogeneity in the sensitivity of people with asthma.

Demographic and Clinical Characteristics

Demographic features of patients with WEA have been compared with both other adults with asthma (17, 21, 25) and other cases of work-related asthma (6, 26). The studies noted vary considerably in their findings regarding distribution by sex, age, race/ethnicity, and cigarette smoking history. This heterogeneity of findings could be due to differences in study setting, case criteria, and other methodological features.

A limited number of studies have examined clinical characteristics of patients with WEA (Appendix EC). From clinical series in which SIC was used to separate WEA from OA, investigators found similar asthma severity scores (10, 29) and daily dose of inhaled corticosteroids (ICS) (29) for both conditions, suggesting similar disease severity. Also, the level of nonspecific airway hyperresponsiveness was either similar (11, 29) or lower (10) in WEA. From surveillance for WRA in the United States, emergency room visits and hospitalizations for asthma were equally common for WEA and OA cases (26).

Epidemiologic surveys conducted among HMO members with asthma have documented that the proportion of symptomatic days is higher among individuals with WEA than in those who do not experience worsening of asthma symptoms at work (17, 21). However, the level of asthma severity derived from medical records was lower than that obtained through self-reporting (17). Moreover, the use of maintenance medications was similar in subjects with or without WEA despite higher rates of symptoms in WEA (17, 21). Interestingly, the need for continuous asthma treatment was more frequent in subjects with WEA as compared with other subjects with asthma without OA in a study based on the Finnish health insurance register (25). The rates of asthma exacerbation requiring specific treatment (21, 30), doctor visit (30), or emergency room admission (30) were higher in subjects with WEA as compared with those of other subjects with asthma in some studies, but not in other studies (9, 17). In a recent study based on data provided by Quebec's Public Health Insurance Plan (11), subjects with WRA—including both WEA and OA—visited a physician or an emergency department because of their asthma and were hospitalized more frequently than subjects with asthma without WRA. WEA was not associated with a higher rate of exacerbations as defined in this study when compared with OA. In both groups, medical resource utilization decreased after removal from exposure to the causal work environment.

A single study has explored the long-term outcome of WEA cases that were defined by the presence of work-related symptoms and a negative SIC test to occupational agents (29). Asthma symptoms, functional indices, and sputum cells were re-assessed in a limited group of patients with WEA and "immunologically-mediated OA" at an interval of 1 to 4 years after the diagnosis had been ascertained by SIC (29). All the patients with WEA and all but one of the patients with OA were removed from the work exposure that caused their symptoms. The patients with WEA and patients with OA showed significant and equivalent improvements in symptom scores. Subjects with WEA showed a trend toward less improvement in airway hyperresponsiveness to methacholine and smaller reduction in the dose of ICS as compared with OA cases.

TABLE 1. PREVALENCE OF WEA FROM STUDIES CONDUCTED IN THE GENERAL POPULATION OR GENERAL HEALTH CARE SETTINGS

Reference	Country	Study Setting and Number of Participants (*% of eligible*)	Criteria for Asthma	No. Asthma Cases	Age (*yr*)	Timing of WEA	Criteria for WEA (Self-Reported on Questionnaire Unless Indicated Otherwise)	WEA Prevalence	
								In All Adults with Asthma	In Working Adults with Asthma
Abramson 1995 (19)	Australia	FU 589 with asthma sx, from G pop survey (74%)	SR asthma dx	159	mean 43	Ever	Respiratory sx at work associated with particular job	20%	NA
Blanc 1999 (14)	Sweden	FU 1,562 in G Pop study (ECRHS) (65%)	SR asthma and BHR	160	20–44	Ever	Being at work ever makes chest tight or wheezy	38%	NA
Bolen 2007*† (18)	USA	FU 95 employed asthma cases in HMO (25%)	Asthma dx by medical record	95	18–45, mean 34	Current, tested 3 wk	Researchers judged pattern of serial peak expiratory flow rate consistent with WEA	NA	14%
Caldeira 2006* (15)	Brazil	FU 1,922 in birth cohort (93%)	SR asthma sx and BHR	227	23–25	Ever	Pre-existing asthma worsened by exposure at work, based on interview information	13%	NA
Goh 1994 (20)	Singapore	802 asthma cases in large primary care clinics (63%)	Asthma dx by medical record	802	20–54	Current	Work environment is asthma trigger	27%	NA
Henneberger 2002 (21)	USA	1,461 asthma cases enrolled in HMO (72%)	Asthma rx or care by medical record	1,461	18–44	Current job	Current work environment makes asthma worse	25%	NA
Henneberger 2003 (16)	USA	664 from random sample survey of G Pop (62%)	SR asthma dx and current rx	42 (28 employed)	18–65, mean 42	Last 12 mo	Coughing or wheezing is worse at work than away from work	14%	21%
Henneberger 2006*† (17)	USA	598 asthma cases identified in HMO records (61%)	Asthma care and dx by medical record	598 (557 employed)	18–44	Last 12 mo	Combination of relevant exposure as judged by researchers and SR work-related sx or medication use	23%, or 21% if more stringent criteria‡	24%, or 22% if more stringent criteria‡
Johnson 2000* (22)	Canada	FU 2,974 in G Pop study (ECRHS) (39%)	SR asthma dx	106 (adult onset)	20–44	Current job	Wheezing or dyspnea at or after work in current job	34% wheezing 31% dyspnea	NA
Johnson 2006* (23)	Australia	5,331 in G Pop study (ECRHS) (37%)	SR asthma dx	694 (employed)	18–49	Current	Asthma better on weekends or holidays	NA	18%
Mancuso 2003 (24)	USA	Prospective study of 230 persistent asthma cases in primary care practice (39%)	Asthma dx by medical record	102 (employed)	18 or older, mean 39	Current job	Asthma made worse by workplace conditions	NA	58%
Saarinen 2003* (25)	Finland	1,925 asthma cases in NHI system (74%)	Asthma dx by medical record	969 (employed)	20–65, mean 43	Past month	Asthma sx caused or worsened by work at least weekly in past month	NA	20%

Definition of abbreviations: BHR = bronchial hyperresponsiveness; dx = diagnosis; ECRHS = European Community Respiratory Health Survey; FU = follow up; G Pop = general population; HMO = health maintenance organization; NA = not applicable; NHI = national health insurance; rx = medications; SR = self-reported; sx = symptoms.

* OA determined unlikely when WEA cases identified.

† The participants in the study by Bolen and coworkers in 2007 (18) were a subset of the participants in the study by Henneberger and colleagues in 2006 (17), but different methods were used to determine WEA status in the two studies.

‡ Thirteen study participants with asthma judged not to have had relevant workplace exposures were still assigned WEA status because they had reported an asthma–work relationship in three different places on the survey questionnaire. If the criteria for WEA were made more stringent by requiring evidence of exposure, then the prevalence was 21% (rather than 23%) among all adults with asthma and 22% (rather than 24%) among working adults with asthma (17).

WEA subjects tended to show a decrease in sputum neutrophil counts, while those with OA had a trend toward a decrease in sputum eosinophils.

Socioeconomic Impact

Researchers using data from the large multinational European Community Respiratory Health Survey have demonstrated that adults with asthma are at a greater risk for changing jobs due to breathing problems than adults without asthma (31). Also, these job changes were associated with occupational respiratory exposures determined by both a job-exposure matrix and self-reports of exposure to vapors, gas, dust, or fumes.

While the financial and social consequences of OA have been quite extensively characterized (32, 33), the socioeconomic impact of WEA has received little attention until recent years. Available studies differed in several important aspects, including target populations and criteria used for defining WEA (6, 9, 10, 17, 21, 25, 26, 29, 30, 34, 35). Available data allowed for comparing WEA with "asthma unrelated to work" (6, 9, 21, 25, 30, 34, 35), with OA (6, 10, 26, 29, 34), or with both conditions (6, 34). Studies have found that WEA is associated with similar rates of unemployment as compared with OA, ranging from approximately 30% to 50% (10, 34) (Table 3). Job changes due to asthma were equally (29, 34) or less (6, 10, 26) common in WEA than in OA.

TABLE 2. REVIEW OF SELECTED PAPERS ON TYPES OF JOBS AND EXPOSURES ASSOCIATED WITH WEA

Reference	Country	Methods to Determine Jobs and Exposures	Study Setting and No. of Participants (% of eligible)	No. Asthma Cases	No. with WEA	Types of Jobs and Exposures Associated with WEA
McClellan 1990 (28)	New Zealand	SR exposures that affected asthma and ability to work	93 sequential cases in asthma clinic (67%)	93 (82 ever employed)	14	Second-hand smoke and dust
Tarlo 1995 (6)	Canada	Records from workers' compensation files	609 workers' compensation claims for OA (100% of records in 4 yr)	527	234	• 67% of WEA cases exposed to irritants • Most common irritants: paints, solvents, calcium oxide, acids, ammonia, cigarette smoke, glutaraldehyde, welding fumes • 40% of WEA cases—accidental exposure or spill • Fewer sensitizers and more irritants than OA cases
Blanc 1999 (14)	Sweden	Work in high-risk jobs (defined a priori by JEM) and SR exposures	FU 1,562 in G Pop study (ECRHS) (65%)	160	61	• High-risk jobs by JEM: lab technicians, medical technicians, farmers, firefighters, welders, cleaners, bleachers, bakers, spray painters, cabinet makers, carpenters • SR exposure: second-hand smoke at work
Henneberger 2002 (21)	USA	Industry of current job	1,461 asthma cases enrolled in HMO (72%)	1,461	367	Wholesale and retail trade, public administration, transportation, and public utilities.

Saarinen 2003 (25)	Finland	Occupations with exposure (defined a priori by JEM) and SR workplace exposure in current job	1,925 asthma cases in NHI system (74%)	1,925 (969 employed)	191	• Exposure to dust, gas, or fumes by JEM
						  • Occupations with probable exposure: manufacturing, agriculture, cleaning, waste handling, hairdressing
						  • Occupations with possible exposure: transport, sales, military, some service jobs
						• SR exposures at work: dusts, chemicals, abnormal temperatures, poor indoor air quality, physically strenuous work

Goe 2004 (26)	USA	Surveillance case reports indicated occupation, industry, and likely agent	1,101 work-related asthma cases from SENSOR surveillance (100% of cases in 3 yr)	1,101 (all work-related asthma cases)	210	• Most common occupations: technical, sales, and administrative support; managerial and professional specialty; operators, fabricators, and laborers • Most common industries: services; manufacturing; public administration • Most common agents: mineral and inorganic dust; indoor air pollutants; chemicals not otherwise specified • Differed from OA cases
Berger 2006 (27)	USA	Jobs and SR asthma triggers	301 low-income patients with asthma in medical center (78%)	301	213	• Jobs with highest % WEA: security guard or police, janitor, garment or textile worker • Asthma triggers at home or work reported by > 50% of subjects: animals; chemicals such as cleaning products, paints, solvents; dust; second-hand cigarette smoke; gases, fumes, odors, or smoke; perfume; exercise; very cold air; hot, smoggy, humid or polluted outdoor air; strong emotions, including stress
Henneberger 2006 (17)	USA	Researchers reviewed job descriptions and assigned separate exposure scores for sensitizers and irritants	598 asthma cases identified in HMO records (61%)	598 (557 employed)	243 with work-related sx or medication use	% reporting work-related sx or medication use increased with sensitizer/irritant exposure score ($P = 0.07$ for trend)

Definition of abbreviations: ECRHS = European Community Respiratory Health Survey; FU = follow up; G Pop = general population; HMO = health maintenance organization; JEM = job-exposure matrix; NHI = national health insurance; SENSOR = Sentinel Event Notification Systems for Occupational Risks; SR = self-reported; sx = symptoms.

When compared with "asthma unrelated to work," the rate of unemployment was similar in WEA (30, 34), and evidence for job changes was mixed with findings that they were either more (34) or less (6) common in subjects with WEA (Table 3). Most available studies (9, 17, 30), with one exception (21), found that the number of lost workdays (i.e., absenteeism) was similar in subjects with WEA and asthma unrelated to the work environment. Impairment in work effectiveness (i.e., presenteeism) has been specifically assessed in one study (36), which found that subjects with asthma with WRA symptoms showed a slight reduction in self-reported ability to work (graded on a scale from 0% to 100%) compared with those who did not report worsening of asthma at work.

Only two studies have attempted to evaluate the impact of WEA on labor-derived income (10, 34) (Table 3). Both studies were case series from specialty clinics where patients were referred for suspected work-related asthma, and further evaluation determined whether the cases were OA or WEA or neither. In these settings, WEA cases most likely had persistent work-related symptoms rather than short periods with symptoms related to work. These studies found that the self-reported frequency and relative magnitude of reduction in

TABLE 3. WORK DISABILITY AND FINANCIAL OUTCOMES IN SUBJECTS WITH WEA COMPARED TO OTHER ASTHMA CASES

Outcomes	Reference	Country	Study Setting and Number of Participants (*% of eligible*)	Asthma Unrelated to Work (n)*		Work-exacerbated Asthma and Relationship to Other Cases (n)*		Occupational Asthma (n)*
Unemployment	Cannon 1995 (34)	UK	178 asthma cases referred to specialized clinic for suspected OA (79%)	32%† (65)	=	31% (26)	=	39% (87)
	Larbanois 2002 (10)	Belgium	157 asthma cases referred to specialized clinic for suspected work-related asthma (87%)	NA		46% (71)	=	38% (86)
	Breton 2006 (30)	USA	8,628 adult participants in 2,001 (40%) and 7,429 in 2,002 (66%) in G Pop study (BRFSS)	38% (1,871)	=	43% (133)		NA
Job/employer change	Cannon 1995 (34)	UK	178 asthma cases referred to specialized clinic for suspected OA (79%)	54%† (65)	<	88% (26)	=	90% (87)
	Tarlo 1995 (6)	Canada	609 workers' compensation claims for OA (100% of records in 4 yr)	62%† (58)	>	42% (234)	<	63% (235)
	Larbanois 2002 (10)	Belgium	157 asthma cases referred to specialized clinic for suspected work-related asthma (87%)	NA		54% (71)	<	72% (86)
	Goe 2004 (26)	USA	1,101 work-related asthma cases from SENSOR surveillance (100% of cases in 3 yr)	NA		17% (210)	<	33% (891)
	Pelissier 2006 (29)	Canada	FU 28 work-related asthma cases previously diagnosed in specialized clinic (% of eligible not stated)	NA		100% (10)	=	94% (18)
Lost workdays	Tarlo 2000 (9)	Canada	310 adult-onset asthma cases referred to asthma clinic were employed (71%)	Mean ± SD, 32 ± 80 d (259)	=	28 ± 42 (51)		NA
	Henneberger 2002 (21)	USA	1,461 asthma cases enrolled in HMO (72%)	12% ⩾ 1 d missed in past 4 wk (1,094)	<	19% (367)		NA
	Breton 2006 (30)	USA	8,628 adult participants in 2,001 (40%) and 7,429 in 2,002 (66%) in G Pop study (BRFSS)	22% unable to do usual activities in past 12 mo (544)	=	22% (47)		NA
	Henneberger 2006 (17)	USA	598 asthma cases identified in HMO records (61%)	Mean ± SEM 1.9 ± 0.3 d in past 12 mo (462)	=	2.8 ± 0.7 (136)		NA
Work ability (self assessed)	Balder 1998 (36)	Sweden	FU 332 employed adults with asthma from primary and specialized clinics (79%)	Median value 100% (143)	>	95% (189)		NA
Loss of income ‡	Cannon 1995 (34)	UK	178 asthma cases referred to specialized clinic for suspected OA (79%)	35%† (65)	<	62% (26)	=	55% (87)
	Larbanois 2002 (10)	Belgium	157 asthma cases referred to specialized clinic for suspected work-related asthma (87%)	NA		59% (71)	=	63% (86)

Definition of abbreviations: BRFSS = Behavioral Risk Factor Surveillance System (Massachusetts, 2001–2002); FU = follow up; G Pop = general population; HMO = health maintenance organization; NA = data not available; SENSOR = Sentinel Event Notification Systems for Occupational Risks.

* Number of subjects in each sub-group in parentheses. The judgment that outcomes were = , > , or < was based on statistically significant differences ($P \leqslant 0.05$).

† Subjects with "asthma unrelated to work" were recruited among patients who were initially evaluated for possible work-related asthma.

‡ Expressed as the prevalence of reported loss of income among studied subjects.

earnings were similar in WEA and OA. A study conducted in Belgium found that the proportion of workers reporting a disease-related reduction of earnings was similar in WEA (59%) and OA (62%) (10). The median income loss was similar in the two conditions: 23% and 22% reduction from initial income, respectively. These findings confirmed those of an earlier study in the United Kingdom (34). Also, the earlier study documented that a self-reported reduction of income was more common in

subjects with WEA (62%) and OA (55%) than in those with "asthma unrelated to work" (35%) (34).

The psycho-social impact of WEA has almost never been evaluated. A recent study, conducted among patients with asthma enrolled in a health maintenance organization in the United States, compared quality of life (QoL) in subjects with WEA and those with asthma unrelated to work (35). QoL was based on responses to the Marks Asthma Quality of Life Questionnaire (37, 38). Participants with WEA had statistically significant lower scores for overall QoL and for the scales pertaining specifically to "mood disturbance," "social disruptions," and "health concerns," even after controlling for relevant covariates.

PATHOPHYSIOLOGICAL MECHANISMS OF OCCUPATIONAL EXPOSURES ASSOCIATED WITH WEA

Experimental Studies with Animals

Asthma has been extensively studied through allergen-driven animal models that have helped clarify the immunological mechanisms that underlie the induction of allergic asthma (39), primarily in models focused on the development of asthma rather than the exacerbation of established pre-existing asthma. The complex networks involving cytokines, chemokines, and lipid mediators have been explored in relationship to initial allergic sensitization, and the development of eosinophilic airway inflammation, airway hyperresponsiveness, and airway remodeling (40). The bulk of the research performed on ovalbumin, ragweed, dust mite, or other allergen-driven murine models does not provide much insight into the pathogenesis of WEA, which less likely involves solely allergen-driven immune-mediated mechanisms of airway inflammation and bronchospasm, and commonly involves relatively low-level multiple irritant or mixed irritant/allergen exposures. Animal models of asthma based on stimuli that act through direct activation or injury of airway cells such as high irritant exposures and mixed allergen/irritant exposures are more pertinent to WEA but are less explored. Exposure to relatively high concentrations of oxidants such as ozone, sulfur dioxide, nitrogen dioxide, and chlorine has resulted in airway hyperresponsiveness, airway remodeling, and goblet cell metaplasia, changes compatible with asthma and/or chronic bronchitis (41–44). The mechanisms of these changes are more likely linked to activation of sensory nerves, epithelial cells, or cells of the innate immune system. Neural responses and neurogenic inflammation may be triggered by transient receptor potential (TRP) channels that transduce responses to a variety of so-called irritants, changes in osmolarity of epithelial lining fluid, and changes in temperature (45, 46). Epithelial responses to leukotrienes or oxidant stress may result in the synthesis of a variety of proinflammatory molecules such as interleukin-8 and may cause the proteolytic cleavage of pro-forms of various growth factor ligands such as heparin-binding epidermal growth factor (47, 48). Activation of the Toll-like receptor-4 (TLR-4) by lipopolysaccharide may lead to ADAM-17 activation and shedding of transforming growth factor-α, another epidermal growth factor receptor ligand, and cause epithelial repair and goblet cell differentiation (49).

Tissue damage and the resulting generation of "alarmins" is increasingly recognized to lead to activation of the innate immune system, in some cases by mechanisms that involve TLRs (50). Such mechanisms of inflammation are of particular relevance to WEA where the stimuli causing worsening of asthma are less clearly linked to allergic mechanisms. Also, interactions between allergen-driven airway inflammation and other stimuli such as ozone, nitrogen dioxide, and diesel exhaust particles likely are common, and animal models have shown that such exposures can damage the airway epithelium, induce oxidant stress, and enhance airway responses to allergens (43, 51–53). Recent research with mice suggest that the sensory nerve activation in the airways might play an important role in the response to common asthma triggers like cigarette smoke and chlorine gases, exposures that can contribute to WEA (54).

Human Studies

Human exposure chamber studies. This section (and the related Appendix ED) include examples, but not an exhaustive review, of controlled exposure studies in subjects with asthma that elaborate the effect of exposures associated with WEA. Appendix ED provides more detail and references for the following exposures: ozone, diesel, second-hand smoke, endotoxin, sulfur dioxide, hydrogen sulfide, acid aerosols, chlorine, scented products and perfumes, acetaldehyde, physical factors (cold dry air, exercise), and volatile organic compounds. The responses reported to these agents included inflammatory changes, increased airway responsiveness, reduced flows, and symptoms.

Asthma medications can reduce responses. Indeed, several challenge studies have shown that changes in airflow limitation induced by exposure (e.g., to sulfur dioxide, endotoxin, and physical factors) can be reduced or prevented with bronchodilators (55–57), suggesting a possible management component for individuals with asthma in these environments, in conjunction with overall asthma control strategies and exposure controls.

Inflammatory changes induced by exposure to occupational agents. There are a limited number of studies that looked at inflammatory changes in subjects with WEA after exposure to occupational agents, predominantly sensitizers. To date, these studies have usually relied on SIC to determine which patients with work-related asthma symptoms had OA versus WEA, with these cases characterized by positive and negative SIC results, respectively. The majority of subjects with OA show an eosinophilic type of inflammation after exposure to the causal agent in the workplace (58, 59) or in a laboratory (60–62). After exposure at their workplace, subjects with WEA have shown no change (58) or a neutrophilic type of airway inflammation (59). After exposure in the laboratory to specific occupational sensitizers, the majority of subjects with WEA have shown no change in airway inflammation, and a few have shown an increase in sputum eosinophilia (61, 62). The numbers of studies and subjects have been small, and the WEA subjects with increased sputum eosinophilia may have been misdiagnosed.

Long-term airway effects of nonsensitizing exposures. Exposures relevant to WEA that may cause chronic effects include endotoxins; organic and inorganic dusts; fumes from chemicals in cleaning products; coolants; and gases such as ozone, sulfur dioxide, and ammonia. Although most studies have not specifically assessed long-term effects on human asthma severity, there are known chronic airway effects that may be of greater clinical significance in workers with asthma. Chronic ozone exposure has been associated with pulmonary function changes reflective of small airway disease among nonsmokers (63). These findings could impact the long-term prognosis of airway disease among workers with asthma exposed to ozone, either among outdoor workers as a component of air pollution, or in occupations such as welders and water bottlers with ozone exposure. Other outdoor air pollutants such as particulates and indoor pollutants such as second-hand smoke are also associated with development of fixed chronic airway disease (64). Workplace exposures to dust and fumes have been associated with an increased risk of airway disease, with an estimated 15% of COPD cases having an occupational contribution (4). Endotoxin similarly has been

implicated in chronic obstructive lung disease in settings such as the cotton industry (byssinosis) (65) and in swine confinement workers (66). Nonoccupational asthma exacerbations, often attributed to respiratory viral infections, have been associated with excess lung function loss in adults with asthma (3, 67). Similarly, it is possible that persistent work exposure may lead to excess lung function loss in WEA cases, although this remains to be demonstrated.

CLINICAL APPROACH

There are limited clinical studies addressing the clinical evaluation and diagnosis of WEA. An expert panel assembled by the ACCP recently published a consensus document on work-related asthma (5). Conclusions from that publication related to the diagnosis and management of WEA are briefly summarized here.

WEA should be considered in any patient with asthma that is worsening and/or who has WRA symptoms. The initial diagnostic step is to clarify whether the patient has asthma. It is especially important to clarify the diagnosis of asthma in settings where work exposures may be causative or contributing factors, and management decisions may involve a worker's job. The presence of asthma prior to the current work environment should be assessed based on the patient's symptoms, medical history including allergies and childhood asthma, and medication usage. The identification of concurrent asthma has been most readily accomplished in settings where SIC is commonly used, and cases who present with work-related symptoms and asthma that started after entering the worksite of interest are classified as OA if test results are positive and WEA if results are negative. In other settings, the identification of concurrent asthma is assumed to be very difficult, and only cases of pre-existing asthma are considered at risk for WEA. For example, this approach is used by the SENSOR surveillance system in the United States (12).

The diagnosis of WEA depends on demonstrating a relationship between work exposures and asthma exacerbations, most commonly documented by changes in symptoms (e.g., frequency, severity) or medication use temporally related to work. More severe exacerbations may additionally be documented by increased health care visits and/or objective physiologic changes related to work. In one study, researchers observed that about half of WEA cases had serial PEFR measurements that were more variable while working compared with periods away from work, although these measurements cannot be used to differentiate WEA from OA (68). Immunologic testing can identify sensitization to specific environmental and workplace allergens, which can assist diagnosis and management.

Identification of exacerbation triggers is important both for confirming WEA and for reducing or eliminating harmful conditions to prevent future problems in the index case and coworkers. Factors or conditions at work that can exacerbate asthma should be assessed, including dusts, fumes, particles, environmental allergens, irritant chemicals, cold or dry air, physical exertion, or viral infections, most commonly from a careful occupational history. Sources of information that help to identify causes at work include material safety data sheets (also called MSDS), workplace site visits, industrial hygiene reports, symptoms among coworkers, and information about comparable workplaces. However, identification of a specific causative agent for WEA is often not possible, and mixed exposures are common. Nonwork factors that can exacerbate asthma, such as viral infections and environmental allergies, should also be evaluated.

WEA should be distinguished from OA (69–71), which can be challenging when the worker has left the suspect job. Transient work-related worsening of asthma on a single occasion or a few occasions is common and usually easily explained and recognized. The evaluation of patients when work-related symptoms are recurrent or prolonged is often similar to the work-up of a patient with possible OA, requiring a more detailed investigation and possibly referral to a specialist. After onset of sensitizer-induced OA, subsequent asthma attacks due to re-exposure to the causative agent is usually considered a recurrence of the OA rather than a new case of WEA. This distinction is especially relevant for medico-legal purposes, most notably workers' compensation. However, workers with prior OA may also develop exacerbation due to agents at work other than those that caused the OA.

Data on the management of WEA are very limited. The goal of treatment is to minimize asthma exacerbations by reducing work exposures (e.g., by limiting sources of exposure, improving ventilation) and optimizing standard medical management with nonwork environmental control measures and pharmacologic treatment. The patient may be able to stay at the same job with reduced exposures, depending on the severity of asthma and extent of exacerbating factors at work, but a job change to a workplace with fewer triggers may be necessary if this approach fails to adequately prevent work-related exacerbation of symptoms.

PREVENTION

Although evidence-based information is lacking, WEA can, by definition, be prevented by intervention at different times in the disease process: primary prevention before the onset of disease, secondary prevention early in the course of the disease, and tertiary prevention once the illness has fully manifested itself. The fundamental activities of prevention resemble those of disease management: reduce work exposures and optimize standard medical management. The informed caregiver can contribute by always considering the work environment of the patient with asthma as a potential source of symptom triggers. This includes pre-placement evaluation and education to help the patient anticipate and respond to problems in a new job or in a modified work setting at an existing job.

Reduction or elimination of work exposures can be accomplished in several ways, and can contribute to primary, secondary, and tertiary prevention. Occupational hazards begin at a source, move through the work environment, and then impact the worker. The hierarchy of control options follows this same sequence. It is inherently beneficial to prevent a harmful exposure before it happens. This can be achieved at the source by modifying the process to eliminate the asthma trigger or to substitute another material for it. At the environmental level, improved ventilation can remove an offending exposure before it is inhaled. Finally, the individual with asthma can use personal protection in the form of a respirator. "Exposures" that cause asthma symptoms can include exercise and extremes in temperature, so modification of the physical demands of the job or the heating and cooling of the work environment may also play a role in prevention of WEA. Most of these prevention activities are controlled by the employer, and improved productivity and reduction of presenteeism may serve as motivators to pursue these interventions (72).

If an employer's good faith reasonable accommodation efforts cannot adequately reduce exposures, primary prevention may sometimes make it necessary to exclude an adult with asthma from certain jobs with frequent uncontrollable asthma triggers. Similarly, secondary and tertiary prevention can be realized by re-assigning a worker with WEA to a different job. The success of this approach depends on the availability of such an area where the asthma patient can work. In the

absence of an alternative work area, the adult with asthma will be excluded or removed from the worksite entirely. When a WEA case can no longer tolerate a work setting, the clinician and patient should carefully balance the potential benefit of removal from work with the benefits (financial and psychological) of continued working (73).

Surveillance facilitates awareness of the need for prevention measures. Exposure surveillance can reveal when exposure controls are not properly functioning and quantify exposure levels associated with identified WEA cases. Medical surveillance in high-risk worksites can play an important role in secondary worker-oriented prevention by identifying early cases of WEA.

Policy or regulatory intervention is also important, and can impact groups of workers (74). Exposure control policies, such as those of corporate or governmental organizations, can lead to a reduction in exposures that exacerbate asthma. Policies concerning work removal, work rotation, or compensation can influence whether an individual leaves the workplace and the availability of healthcare. Workers' compensation policy can significantly impact the motivation of workers to obtain treatment for significant exacerbations. In the United States, the Americans with Disabilities Act mandates that employers make "reasonable accommodation" for individuals with disabilities, such as asthma (75). However, the extent of control necessary for one affected worker may not be feasible throughout an entire worksite. Government policies that require the reporting of WEA as an occupational illness can promote wider awareness of WEA, and facilitate risk assessment and prevention (12, 76, 77).

RESEARCH NEEDS

This review of the literature highlights the substantial prevalence and impact of WEA. Research to better define risk factors, biologic mechanisms, and outcomes should lead to improved diagnostic, treatment, and preventive strategies for WEA. The following research would address these needs.

1. Better exposure assessment methods are needed to identify and characterize the complex exposures in different occupations, industries, and work settings that contribute to WEA, including approaches to estimate/model these exposures for incorporation into clinical and epidemiologic studies.
2. Characterize the nature of asthmatic responses to common work triggers in human subjects with different asthma phenotypes through controlled and workplace exposure studies.
3. Characterize the natural history of WEA, including clinical, physiological, and socioeconomic outcomes.
4. Conduct intervention studies to evaluate the effectiveness of different preventive and management approaches on the development and outcomes of WEA, including preemployment advice or career counseling, interventions to reduce work exposures, and strategies to optimize asthma care.
5. The pathophysiological mechanisms that can potentially contribute to the development of asthma symptoms and WEA, especially neurogenic inflammation and epithelial response to oxidant stress, should be further investigated by assessing the effects of irritant exposures and the interactions between irritants and allergens in animal models of chronic asthma.

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Members of the subcommittee:
Paul K. Henneberger, M.P.H., Sc.D. (*Chair*)
Carrie A. Redlich, M.D., M.P.H.
David B. Callahan, M.D.
Philip Harber, M.D., M.P.H.
Catherine Lemière, M.D., M.Sc.
James Martin, M.D.
Susan M. Tarlo, M.B. B.S.
Olivier Vandenplas, M.D.
Kjell Torén, M.D., Ph.D.

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