

Pulmonary Perspective

The Healthy Worker Effect in Asthma

Work May Cause Asthma, but Asthma May Also Influence Work

Nicole Le Moual^{1,2}, Francine Kauffmann^{1,2}, Ellen A. Eisen^{3,4}, and Susan M. Kennedy⁵

¹INSERM U780, Villejuif, France; ²Faculty of Medicine, Université Paris-Sud, IFR69, Villejuif, France; ³Harvard School of Public Health, Boston, Massachusetts; ⁴School of Public Health, University of California, Berkeley, California; and ⁵School of Occupational and Environmental Hygiene, University of British Columbia, Vancouver, British Columbia, Canada

Despite the increasing attention to the relationship between asthma and work exposures, occupational asthma remains underrecognized and its population burden underestimated. This may be due, in part, to the fact that traditional approaches to studying asthma in populations cannot adequately take into account the healthy worker effect (HWE). The HWE is the potential bias caused by the phenomenon that sicker individuals may choose work environments in which exposures are low; they may be excluded from being hired; or once hired, they may seek transfer to less exposed jobs or leave work. This article demonstrates that population- and workplace-based asthma studies are particularly subject to HWE bias, which leads to underestimates of relative risks. Our objective is to describe the HWE as it relates to asthma research, and to discuss the significance of taking HWE bias into account in designing and interpreting asthma studies. We also discuss the importance of understanding HWE bias for public health practitioners and for clinicians. Finally, we emphasize the timeliness of this review in light of the many longitudinal "child to young adult" asthma cohort studies currently underway. These prospective studies will soon provide an ideal opportunity to examine the impact of early workplace environments on asthma in young adults. We urge occupational and childhood asthma epidemiologists collaborate to ensure that this opportunity is not lost.

Keywords: epidemiology; asthma; occupational exposure; healthy worker effect

Despite the increasing attention to the relationship between asthma and work exposures, in both clinical and public health practice (1, 2), occupational asthma remains underrecognized by physicians, patients, and occupational health policy makers. This may be due, in part, to the fact that traditional approaches to studying asthma in populations cannot adequately take into account the possibility of "reverse causation"—that is, the possibility that the presence of asthma symptoms may influence job choices or changes in exposure. Concurrently, numerous studies of asthma in children have focused on potential environmental risk factors for asthma in home, school, and community exposures (3, 4). The phenomenon of reverse causation may also occur in these studies, because symptoms may lead to

changes in exposure (e.g., avoiding household pets), but further complexity arises as some early exposures may in fact be protective.

In the coming years, the children in several ongoing cohort studies will reach young adulthood and enter the workforce. These studies could provide an ideal setting in which to better evaluate the impact of work exposures on exacerbation of preexisting asthma or on the development of new asthma in adults. However, as is the case for occupational asthma epidemiology in general, the follow-up into the workplace of these child cohorts will need to be carefully designed to ensure that the potential reverse causation phenomenon is taken into account.

In occupational epidemiology, this reverse causation phenomenon is called the healthy worker effect (HWE). The HWE is the potential bias caused by the phenomenon that sicker or more sensitive individuals may choose work environments in which exposures are low; they may be excluded from being hired; or once hired, they may seek transfer to less exposed jobs or leave work. This bias has been well described in occupational mortality studies (5, 6). However, although asthma morbidity studies are particularly subject to HWE bias (as we will demonstrate), the impact of this bias in asthma epidemiology has received little attention.

Therefore, our objective for this Pulmonary Perspective is to describe the HWE as it relates specifically to asthma research, and to discuss the significance of this bias for interpreting the results of population-based asthma studies.

OVERVIEW OF THE HWE CONCEPT

The concept of the HWE dates to the 18th century when Ramazzini suggested the presence of selection effects in some jobs, such as miners or cleaners (7). According to Fox and Collier, the HWE was formally described for the first time in 1885 by Ogle who explained that "some occupations may repel, while others attract, the unfit at the age of starting work, and conversely some occupations may be of necessity recruited from men of supernormal physical condition" (8).

The HWE phenomenon often leads, paradoxically, to lower death rates observed in subjects exposed to workplace toxins compared with the general population (5). Thus, the bias generally leads to an underestimation of relative risk for occupational exposure and disease (9).

In mortality studies, the magnitude of downward bias due to the HWE is approximated by how much the expected number of deaths exceeds the observed number, as measured by the standardized mortality ratio (SMR) for all causes of death combined. It is common to observe SMRs of 0.8 to 0.9 in occupational cohort mortality studies, suggesting an underestimation of risk by 10 to 20%. Deficits in SMR for mortality are greater for chronic

(Received in original form March 13, 2007; accepted in final form September 13, 2007)

Supported by InVS/Direction of Labor grant 03-S-ST-A20-08, AFSSET (French Agency of Health Safety, Environment and Work) grant ES-2005-015, EU Framework Program for Research contract FOOD-CT-2004-506378, and the GA2LEN project (Global Allergy and Asthma European Network).

Correspondence and requests for reprints should be addressed to Nicole Le Moual, Ph.D., INSERM U780, Recherche en Épidémiologie et Biostatistique, 16 avenue Paul Vaillant Couturier, 94807 Villejuif Cedex, France. E-mail: lemoual@vjf.inserm.fr

Am J Respir Crit Care Med Vol 177, pp 4–10, 2008

Originally Published in Press as DOI: 10.1164/rccm.200703-415PP on September 13, 2007
Internet address: www.atsjournals.org

nonmalignant respiratory disease and heart disease than for cancer, although HWE bias affects cancer as well (8).

By contrast, there is no single measure of HWE bias in morbidity studies, and evidence of the HWE usually involves documentation of less healthy workers changing or quitting jobs during follow-up (10–12), or is inferred from an absence of an expected association between exposure and disease. In morbidity studies, HWE bias has been shown to be more important for diseases that appear in childhood, present early symptoms, or have a shorter latency between exposure and symptoms (9, 13). Stronger healthy worker selection bias was observed for asthma compared with diabetes (14), rhinitis (15), and chronic bronchitis (16).

COMPONENTS OF HWE BIAS

HWE bias arises from two complementary mechanisms (*see* Figure 1) induced by initial and continuing selection process (5, 9): the selection of healthier workers at hire (healthy worker hire effect) and the interruption, change, or cessation of work by less healthy subjects (healthy worker survivor effect).

Healthy Worker Hire Effect

Selection at hire may be due to (13) selection by the subject (personal choice or in response to medical advice) or selection by the employer; in either case this may be related to health status or perceived risk factors. In general, healthier subjects at lower risk of disease (e.g., nonsmokers or physically strong people) tend to be employed preferentially (6, 17).

Children with asthma may be advised, reasonably, not to pursue job training in dusty occupations, and persons with asthma in general are less likely to be hired into exposed trades. Preemployment screening or posthire placement may be important interventions in preventing exacerbation of preexisting asthma. Yet, selection out of exposed jobs may have negative economic impacts, which can also affect general health status indirectly through reduced socioeconomic position (13).

Healthy Worker Survivor Effect

Once hired, less healthy workers are more likely than healthy coworkers to leave high-exposure jobs, either by transfer or termination. For example, in a Swedish study, subjects who reported illness at hire had a 45% higher risk of being unemployed 7 years later (18). Although this selection away from exposed jobs may protect individual health by reducing the impact of exposure in

a given patient, it remains a source of bias in epidemiology, potentially leading to a false conclusion that the higher exposure jobs are safe.

A decline in health (such as asthma symptoms) could induce the following: behavior modification (e.g., use of masks to reduce exposure), leaving work permanently, transfer to a less exposed job, or temporary removal from exposure as a result of physician intervention (9, 13, 17). If workers who lower their exposures are also more likely to develop clinical asthma, then healthy worker bias will result (9, 19, 20).

Cross-sectional workplace surveys usually include only active workers at the time of the survey, thus introducing both healthy worker hire and survivor bias (9, 13, 20). By contrast, population-based surveys including inactive as well as active subjects are less biased by healthy worker survivor bias provided the information relevant for examining the timing of exposures in relation to potential health impacts is recorded.

Estimating the Impact of Components of HWE Bias in Asthma Epidemiology

Although many asthma epidemiology studies comment on the potential for HWE bias, few are able to estimate the magnitude of the impact of such biases. Table 1 summarizes data from all occupational studies we were able to locate up to the end of 2006 (by searching all available medical literature, starting with keywords and following up using reference lists of identified studies) in which data were provided from which one can infer the magnitude of these two components of HWE bias. As shown, the healthy worker hire effect has seldom been measured directly in asthma, with the exception of the study from Radon and colleagues (21) in adolescents' school-based vocational training (Table 1). More studies have estimated the magnitude of the healthy worker survivor effect with remarkably similar results, most indicating risk ratios of about 2, comparing persons with and without asthma with respect to quitting or changing jobs in a wide variety of work environments.

DETERMINANTS OF HWE BIAS

In General Population Epidemiology

Factors that determine the magnitude of HWE bias have been identified for mortality studies and are likely to impact this bias in morbidity studies as well (9, 13, 22) (Table 2). As discussed above, because persons with asthma may have already made job

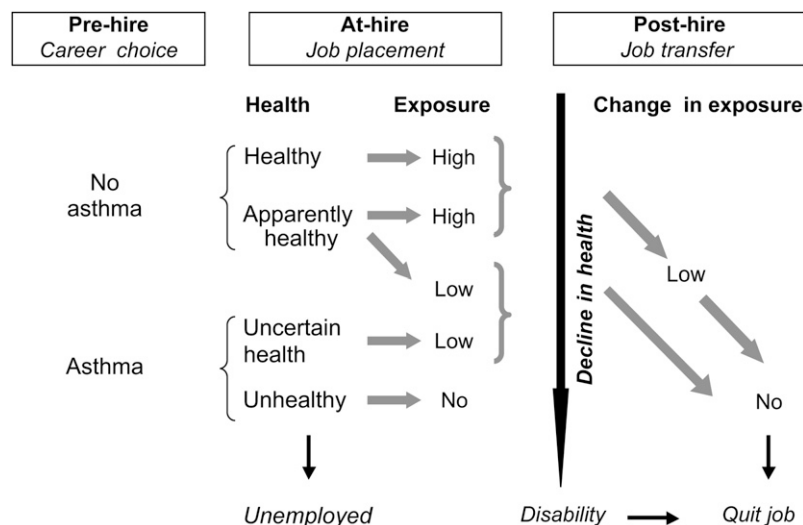


Figure 1. Phenomenon of selection at work. The figure presents selection forces according to health status and periods in the working life (from the career choice until retirement). Arrows depict the evolution of exposure in relation to health status.

TABLE 1. STUDIES ESTIMATING THE MAGNITUDE OF HEALTHY WORKER EFFECT BIAS IN ASTHMA EPIDEMIOLOGY

Study	Study Population*	Study Design	Exposure Metric	HWE Bias, Evidence†
Young Adults				
Kivity and colleagues, 1995 (35)	107,636 Israel soldiers, 18–21 yr	7-yr Follow-up	Soldiers (administrative, technical, combat)	Survivor effect; more job transfer among persons with moderate (71%) vs. mild (52%) asthma
Kennedy and colleagues, 1999 (11)	Canadian apprentices: 82 machinists, 152 others; mean age, 24 yr	2-yr Follow-up study	Machinists (exposed to MWF) compared with unexposed apprentices in other occupations	Survivor effect; 15% of machinists quit trade within 2 yr vs. 3% of unexposed workers ($P < 0.001$)
Monso and colleagues, 2000 (12)	769 Canadian apprentices in animal health, pastry, and dental hygiene; age, 20 yr	4-yr Repeated measures study	Exposure to high-molecular-weight agents	Survivor effect; OR for quitting work was 1.6 (0.9–2.7) for shortness of breath, 1.4 (0.9–2.4) for symptoms of asthma, and 0.9 (0.4–1.9) for physician-diagnosed asthma
Iwatsubo and colleagues, 2005 (10)	French women apprentices: 280 hairdressers, 250 others; mean age, 17 yr	2-yr Follow-up study	Hairdressers potentially exposed to persulfates vs. unexposed office workers	Healthy hire effect; hairdresser apprentices had at both initial and final phase of the study significantly fewer symptoms (cough, wheezing, dyspnea; all OR < 0.5), but more BHR (OR, 1.6 [1.0–2.6]) than office apprentices at the final phase of the study
Radon and colleagues, 2006 (21)	1,416 German teenagers in vocational and high school (ISAAC II), 16–18 yr	7-yr Follow-up study	Jobs classified as high exposed (asthmagens), low exposed (irritants), or unexposed by a job exposure matrix	Healthy hire effect; subjects with past asthma symptoms perhaps less likely to choose high-exposed jobs (OR, 0.7 [0.3–1.6])
Adults, Population-based Surveys				
Blanc and colleagues, 2001 (15)	125 Persons with asthma, 175 persons with rhinitis in general California population survey; 18–50 yr	Cross-sectional	Employment	Survivor effect; persons with asthma less active in the workforce after diagnosis (OR, 3.0 [1.1–7.7]) and likely to be unemployed (OR, 1.6 [1.0–2.6]) than those with rhinitis
Henneberger and colleagues, 2003 (37)	474 Subjects with current physician-diagnosed asthma or asthmalike symptoms, U.S.; 18–65 yr	Cross-sectional	Jobs classified as high risk (exposed to asthmagens)/low risk by experts	Survivor effect; higher prevalence of asthma in high-risk jobs compared with low-risk jobs (38 vs. 19%, $P = 0.17$) Lower prevalence of exacerbation of previously identified asthma in high-risk (14.3%) vs. low-risk (23.8%) jobs (OR, 0.6 [0.1–4.3]), but which is not the case for asthmalike symptoms (OR, 3.7 [1.1–11.9])
Turner and colleagues, 2005 (14)	165 Patients with asthma, 283 diabetics, in outpatient clinic, U.K.; 16–60 yr	Cross-sectional study	Exposure to irritants, sensitizers, and physical activity estimated by experts	Survivor effect; persons with asthma compared with diabetics were less likely to be employed a year after diagnosis (OR, 2.1 [1.3–3.5]) and more likely to stop working for illness reasons (35 vs. 18%)
Adults, Occupational Cohorts				
Dosman and colleagues, 1991 (52)	207 Canadian male grain workers (first work), 120 agricultural students	Follow-up: 1 yr later	Grain work	Survivor effect; prevalence of positive skin tests at baseline: 33% (unexposed) vs. 21% (exposed), $P < 0.01$; 1 yr later: 28% (unexposed) vs. 8% (exposed), $P < 0.001$; high turnover, stayers: 33% (unexposed) vs. 19% (exposed), $P < 0.01$
Eisen and colleagues, 1997 (31)	1,705 U.S. male auto workers; mean age, 40 yr	Cross-sectional study with analysis based on pseudo-incidence study	Exposure to straight, soluble, or synthetic metalworking fluid (vs. unexposed assembly) in 2 yr before diagnosis and at time of survey	Survivor effect; persons with asthma more likely to be exposed to synthetics than unexposed before diagnosis (OR, 4.0), and more likely to have moved to unexposed jobs by time of survey than controls ($P < 0.10$)
Zock and colleagues, 1998 (33)	135 Netherlands potato processing workers; mean age, 40 yr	Cross-sectional study	Duration of employment in potato processing with potential exposure to endotoxin and potato antigens	Survivor effect; prevalence of asthma symptoms was higher among subjects who worked less than 5 yr, compared with those who worked longer (22 vs. 9%), as was prevalence of IgE (56 vs. 24%)
Drexler and colleagues, 1999 (34)	110 German workers in electrical equipment plant	5-yr Follow-up study	Potentially exposed to epoxy resins	Survivor effect; sensitized subjects 2.6 times more likely to leave work than subjects without sensitization
Redlich and colleagues, 2002 (40)	75 U.S. auto body shop workers; mean age, 35 yr	1-yr Follow-up study	Auto body shop workers with potential exposure to HDI	Survivor effect; workers who left trade had more baseline symptoms than those who remained at work

Definition of abbreviations: BHR = bronchial hyperresponsiveness; HDI = hexamethylene diisocyanate; HWE = healthy worker effect; MWF = metalworking fluid; OR = odds ratio.

* Study populations includes industry, no. subjects, age, and employment status.

† Results (measure of association).

TABLE 2. DETERMINANTS OF HEALTHY WORKER EFFECT BIAS: CHARACTERISTICS OF THE STUDY POPULATION, OUTCOME, AND SOCIAL ENVIRONMENT THAT INFLUENCE HEALTHY WORKER BIAS

Determinants	Impact on HWE
Employment factors	
Time since hire	Mortality rate increases (HH wears off) as workers are followed longer (5, 23, 26). Opposite trend for asthma, with incidence of new cases highest soon after hire and decreasing with time (31).
Active versus inactive	Active workers have lower mortality than retirees or inactive workers followed over time (38). Incidence of asthma has not been compared between active and inactive person-time or workers.
Time since termination	Mortality rate peaks in the few years after leaving work and then plateaus at a level higher than active workers (53). This trend may also be true for asthma incidence, but has not been studied.
Sociodemographic factors	
Sex	Stronger selection of healthy males into the workforce (HH), but stronger selection out of the workforce for less healthy women (healthy worker survivor effect) (26) in mortality studies. Expect similar trends for asthma..
Age	HH (mortality) is strongest among youngest workers and declines with age (25). By contrast, asthma incidence may be highest among younger new hires (31).
Ethnic groups	HWE (mortality) stronger in nonwhites (13, 22, 25), probably due to higher turnover and higher loss of follow-up in nonwhites compared with whites. Impact in asthma may be similar (for same reasons) or opposite if ethnicity is linked to employment options.
Community unemployment rate	Unemployment rate likely to impact HWE. Willingness of person with asthma to leave job depends on employment options.
Outcome	
Asthma	Stronger HWE in studies of symptomatic chronic conditions, such as chronic respiratory or heart disease, compared with outcomes with longer latency and shorter symptomatic periods (31).

Definition of abbreviations: HH = healthy hire; HWE = healthy worker effect.

change decisions before the start of a cross-sectional epidemiologic study, stronger HWE bias is seen in studies of only active workforces compared with studies that include former and active workers (9). For most disease outcomes, HWE bias is also stronger among populations with a shorter time since first hire (6, 23), and in younger cohorts (13, 24, 25), and this will decline with population age (25). As discussed below, this may not hold true for asthma.

Sex, social class, and ethnicity have also been shown to play a role in HWE bias in other disease outcomes (13, 22), although few asthma studies taking these determinants into account are available. A stronger healthy hire effect for men and a stronger healthy worker survivor effect for women has been reported (26). Lower HWE bias is predicted in times of high unemployment and among lower social classes, where job choices are more constrained (22). However, the effect of these factors on HWE bias varies by sex and socioeconomic factors (18, 27). Evidence indicates that populations with few employment choices (low social class, women, older) will be less affected by HWE bias, suggesting these groups may be less protected (by job change) from adverse health effects of workplace exposures.

In Asthma Epidemiology

Age. Childhood onset asthma is more likely to contribute to the healthy hire effect, whereas adult-onset asthma influences the healthy survivor effect. Among adults who develop asthma related to work exposures, age at onset (time since hire) varies considerably (28–30). One can theorize that new occupational asthma in young adults may be more likely to lead to HWE bias because voluntary job change is easier for young workers than for older workers. However, this has not been well documented, and in fact, in one study, persons with cedar asthma who left employment were older than those who stayed on the job (27).

Atopy. Persons with asthma may select jobs to avoid exposure to allergens (31) or irritants (32), and if hired, may leave work with this kind of exposure (20). Whether this effect depends on atopy is less clear. In a study of reported career preference among adolescents, Radon and colleagues observed that vocational trainees with allergic rhinitis were more likely to prefer less dusty jobs than other teenagers, suggesting a potential healthy hire bias, but this association did not reach significance (21). Among

apprentices, Monso and colleagues observed that hay fever was a significant risk factor for quitting a job with exposure to high-molecular-weight allergens (12). Workers employed for less than 5 years in the potato industry were more likely to be atopic (and to have asthma symptoms) than those employed for a longer duration (33). In a prospective study, workers who were sensitized to acid anhydride were three times more likely to have quit work 4 years later than workers without sensitization (34).

Asthma severity. Among young military recruits, increased job transfer was seen among persons with asthma compared with those without asthma, and this effect was even greater in those with moderate asthma (71% changed jobs) compared with mild asthma (52%) (35). Severity has also been shown to be an important predictor for unemployment, change in jobs, and disability among individuals with asthma (36).

Exacerbation of symptoms at work. In a population-based study, an association between high occupational exposure (compared with low exposure) and work exacerbation of symptoms was observed among subjects with asthma symptoms; this effect was not seen for subjects with physician-diagnosed asthma (37). This lack of association might be due to an HWE bias, if those with a diagnosis of asthma had already taken steps to avoid irritating exposure jobs or otherwise reduce their exposures at work.

RELEVANCE FOR RESEARCHERS AND PRACTITIONERS

Given the potential sources and determinants for HWE bias in asthma epidemiology described above, it is not surprising that researchers and occupational health practitioners often find low rates of asthma among active employees, whether in epidemiologic studies or in surveillance programs. Thus, when planning asthma research, and in interpreting results of asthma studies, one should always anticipate healthy worker bias downwards. In the case of a true positive relationship, this downward bias results in bias toward the null hypothesis of no exposure–response effect. Of course, other explanations for null or inverse associations should also be considered. For example, the lack of association with farming exposure may relate to a protective effect of an associated factor (farming associated with exposure to endotoxin in childhood).

Strategies for Reducing HWE Bias in Asthma Epidemiology

Epidemiologists treat HWE as either a form of confounding or selection bias. Confounding can be reduced in data analysis, whereas selection bias can only be avoided in the design phase of study.

To reduce HWE bias, employment status (currently working vs. not working) could be treated as a simple confounder by adjusting the exposure–response analysis for employment status (23, 38). This adjustment will pose a problem, however, if leaving work is an intermediate factor on the pathway from exposure to disease (5)—for example, if exposure leads to asthma symptoms which precipitate leaving work before the diagnosis of asthma is made. This is the case for healthy worker survivor bias and the potential for this bias is greater in a cross-sectional study than in a prospective study of workers observed over time (9, 17).

To avoid this bias, prospective studies can include a dynamic cohort where subjects enter the study population when they are hired (or even before first employment, as is the case with childhood cohort studies) and are followed even after they leave employment. This study design allows for both adjustment by employment status as a time-varying factor, as well as for the consideration of time-varying exposure windows.

To illustrate the impact of the study design on HWE, consider studies of two agents recognized to cause occupational asthma in some workers; diisocyanates and synthetic water-based metalworking fluids.

In a cross-sectional study of auto body shop workers, spray painters with the highest exposure to hexamethylene diisocyanate (HDI) were compared with indirectly exposed technicians and office workers in the same workplaces. Painters had more HDI-specific lymphocyte proliferation, but no overt cases of clinically apparent diisocyanate asthma were identified (39). One year later, the 15% who had left were found to be younger, and more likely to have a history of asthma and HDI-specific IgG than those who remained at work (40). Thus, a high turnover rate, with susceptible young workers leaving, contributed to the underestimate of asthma prevalence (bias) among HDI-exposed workers. To estimate the correct (unbiased) exposure–response parameter, rather than merely document the presence of the bias, active and inactive workers should be followed longer and reexamined regularly. Because employment status may change over the study period if subjects leave work, this is a time-varying confounder and thus requires a larger sample size and more complex structural equations to model correctly (41, 42).

Synthetic metalworking fluids are also known to cause asthma in exposed populations (11). Yet, in a large cross-sectional study of autoworkers, asthma prevalence was lower among exposed than unexposed workers (43). A reanalysis was designed to address the hypothesis that the absence of a positive association was caused by the self-selection of individuals with asthma out of exposed jobs (31). Employment records were used to define exposure in the 2 years before asthma diagnosis, and allowed the data to be reanalyzed as “pseudoincidence” study, treating exposure and outcome as time-varying covariates in a Cox model. Using this analytic approach reduced the bias, and an elevated relative risk of asthma diagnosis was found among subjects exposed before diagnosis. It is important to note that, although accounting for job transfer reduced HWE bias, it could not be eliminated in this cross-sectional study because inactive workers were excluded at the time of the survey.

Therefore, even in a carefully designed cohort study that includes shorter-term workers and an internal reference group of low-exposure workers, potential for residual HWE bias remains. As described above, when affected workers migrate

to jobs with lower exposure, they leave behind a more resistant population in the high-exposure jobs, introducing the potential for job transfer bias (9). Truncated exposures of symptomatic subjects can potentially distort even comparisons between high- and low-exposed workers in a longitudinal study. This bias can be minimized with appropriate attention to quantifying exposures in relevant time windows, but such detailed exposure quantification is not always feasible. Thus, awareness of the potential for HWE bias in interpreting results remains important despite attempts to reduce the bias in the study design and analysis (6, 9, 13).

Considerations for Public Health Surveillance

The HWE can also bias estimates of the population burden of asthma attributable to work exposures. A review of the 21 asthma studies considered by the American Thoracic Society working group (2) illustrates the difficulty in estimating the occupational contribution to the burden of asthma. First is the frequent lack of time-varying exposure information presented in biologically relevant time windows of exposure. A third of these papers only focused on adult-onset asthma or used job- or work-related exposures at time of asthma onset or in the few years before diagnosis (44, 45). Several studies reported that lifetime work histories had been collected, but the data were not systematically used in analysis. Second, most studies were cross-sectional in design or used only cross-sectional information for the analyses. Other aspects, beyond the HWE, can modify the estimate of the attributable risk, which depends of the outcome considered. Asthma has been defined by questionnaire, bronchial hyper-responsiveness (2), or recently, reimbursement of costs (46). Even more importantly, the specificity of the exposure is often poor. The attributable risk is lower when exposure is based on known asthmagens exposures rather than less specific exposure estimates (47). Evaluating the specific impact of healthy worker effect (i.e., the magnitude of bias) on the population attributable risk has not been attempted.

Surveillance strategies that take into consideration both healthy worker hire and healthy worker survivor bias would provide more accurate estimates of the true population burden relevant for public and occupational health agencies. One approach to occupational asthma surveillance implemented in several U.S. states involved sentinel event notification (i.e., suspected occupational asthma cases) followed by additional active case finding among coworkers at the workplace suspected of having work-related asthma (48). To improve the accuracy of the burden of occupational exposure, this coworker follow-up would need to include not only active coworkers but also former employees.

Similarly, population health surveys increasingly used in many countries as one way of measuring chronic disease prevalence will also underestimate work-related asthma if strategies for taking HWE bias are omitted. For example, both the U.S. National Health and Nutrition Examination Survey and the Canadian National Population Health Survey include questions about asthma and about occupation. However, neither survey is able to generate unbiased estimates of work-relatedness of asthma because they do not query age or job held at the time of onset of asthma symptoms.

Population surveillance protocols that collect data that allow stratification of asthma by age of onset (before or after the start of work), or even better, by job categories (where the job used is the one held at the time of asthma onset), thereby adjusting for HWE bias, will provide more accurate estimates of the population burden of work-related asthma. Relative risk estimates for the association between exposure and asthma clearly increased when analysis was restricted to adulthood asthma (49), especially in relation to severe asthma (50).

Considerations for Clinical Practice

Clinicians may wonder about the relevance of this discussion to clinical work. In fact, one might argue that, at the level of the individual patient, the implications of healthy worker selection, as a population-level phenomenon, is positive for patients—that is, that an asthmatic teenager or young adult is wise to avoid work that may exacerbate asthma, and that an adult who develops asthma related to (or exacerbated by) work is wise to change jobs.

In this light, the impact of the HWE among individuals with asthma is somewhat similar to a phenomenon that may be more familiar to chest physicians, namely the so-called healthy smoker effect (51). This refers to the phenomenon that adolescents who continue to smoke into adulthood may have better lung function (at least in young adulthood) than those who try smoking but never take it up seriously or who quit at a young age, because they are the ones least susceptible to the early effects of smoking.

An important distinction between these two related phenomena is that the choice to smoke is voluntary, whereas the choice of whether or not to work in an “exposed” job is often much less so. Indeed, the outcome of job change for an individual with asthma affected by exposures at work is not always positive if work change results in unemployment or significant loss of earnings, as has been shown to be the case frequently for patients with occupational asthma (14, 15, 36).

However, clinicians do need to be alert to the healthy worker survivor effect in diagnosing occupational asthma and in considering the best management of patients with asthma. Occupational asthma is difficult to diagnose in the absence of a clearly identified sensitizer in the patient’s workplace. Surrogate indicators are often sought, such as evidence that coworkers may be experiencing similar symptoms, but such questioning needs to consider former as well as current coworkers.

The clinician’s role in identifying and counseling patients with asthma with respect to exposure control in workplaces cannot be minimized, even if the only exposure control option is job change. As described above (37), an asthma diagnosis (with, presumably, associated counseling and case management) can be protective for work-related asthma, even if the occupational link is not recognized. Furthermore, because of the potential for HWE bias to obscure exposure–response associations in epidemiology studies, clinicians should not rule out occupational asthma in a patient with a clear clinical presentation because of a lack of supporting epidemiologic evidence.

CONCLUSIONS AND RECOMMENDATIONS

In summary, HWE bias is particularly strong in studies of asthma and its inevitable presence makes it difficult to develop unbiased risk estimates of the magnitude of exposure–response relationships, in working populations or population-based studies. However, it is not a completely intractable problem. As we have argued above, to generate less biased risk estimates, and to better quantify the burden of work-related asthma, the studies should be designed prospectively with follow-up starting before hire and include lifetime information regarding health events (e.g., age of asthma onset), occupational history (initial job training choices, job transfers, and exposure estimates by monitoring or other methods), and taking into account exposure windows in relation to the onset of asthma symptoms. Population surveillance programs should include similarly detailed information about the timing of disease onset in relation to jobs held. Although some might argue that such studies and surveillance systems are not feasible, we suggest that the refinements needed to upgrade existing methods for data collection and

analysis for asthma epidemiology are modest and often within reach.

Importantly, the many population-based birth or childhood cohort studies currently underway to examine risk factors for asthma represent a great opportunity because they have already been designed as prospective studies that will permit the ongoing collection of time-varying exposure and health information as these young people enter the workforce. We recommend that occupational and childhood asthma epidemiologists collaborate to ensure that this opportunity is not lost.

Conflict of Interest Statement: None of the authors has a financial relationship with a commercial entity that has an interest in the subject of this manuscript.

References

1. Chan-Yeung M, Malo JL, Tarlo SM, Bernstein L, Gautrin D, Mapp C, Newman-Taylor A, Swanson MC, Perrault G, Jaques L, *et al.* Proceedings of the first Jack Pepps occupational asthma symposium. *Am J Respir Crit Care Med* 2003;167:450–471.
2. Balmes J, Becklake M, Blanc P, Henneberger P, Kreiss K, Mapp C, Milton D, Schwartz D, Toren K, Viegi G. American Thoracic Society statement: occupational contribution to the burden of airway disease. *Am J Respir Crit Care Med* 2003;167:787–797.
3. Asher MI, Montefort S, Björkstén B, Lai CK, Strachan DP, Weiland SK, Williams H. Worldwide time trends in the prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and eczema in childhood: ISAAC phases one and three repeat multicountry cross-sectional surveys. *Lancet* 2006;368:733–743.
4. Beasley R. The burden of asthma with specific reference to the United States. *J Allergy Clin Immunol* 2002;109:S482–S489.
5. Arrighi HM, Hertz-Picciotto I. The evolving concept of the healthy worker survivor effect. *Epidemiology* 1994;5:189–196.
6. Li CY, Sung FC. A review of the healthy worker effect in occupational epidemiology. *Occup Med (Lond)* 1999;49:225–229.
7. Ramazzini B. Des maladies du travail. Arcier AF, Arcier H, editors. Aysnès, France: Alexitère; 1990. New edition of “Essai sur les maladies des artisans traduit du latin de Ramazzini, avec des notes et des additions, par M. de Fourcroy...” de Fourcroy A-F, translator and editor. 1777. Translation of “De morbis artificum diatriba” (1713).
8. Fox AJ, Collier PF. Low mortality rates in industrial cohort studies due to selection for work and survival in the industry. *Br J Prev Soc Med* 1976;30:225–230.
9. Eisen EA. Healthy worker effect in morbidity studies. *Med Lav* 1995; 86:125–138.
10. Iwatsubo Y, Matrat M, Brochard P, Ameille J, Choudat D, Conso F, Coulondre D, Garnier R, Hubert C, Lauzier F, *et al.* Healthy worker effect and changes in respiratory symptoms and lung function in hairdressing apprentices. *Occup Environ Med* 2003;60:831–840.
11. Kennedy SM, Chan-Yeung M, Teschke K, Karlen B. Change in airway responsiveness among apprentices exposed to metalworking fluids. *Am J Respir Crit Care Med* 1999;159:87–93.
12. Monso E, Malo JL, Infante-Rivard C, Ghezzi H, Magnan M, L’Archevêque J, Trudeau C, Gautrin D. Individual characteristics and quitting in apprentices exposed to high-molecular-weight agents. *Am J Respir Crit Care Med* 2000;161:1508–1512.
13. Chen R, Seaton A. The influence of study characteristics on the healthy worker effect: a multiple regression analysis. *Occup Med (Lond)* 1996; 46:345–350.
14. Turner S, Cherry N, Robinson J. Workplace exposures and employment patterns in adult onset asthmatics and diabetics. *Occup Med (Lond)* 2005;55:287–291.
15. Blanc PD, Trupin L, Eisner M, Earnest G, Katz PP, Israel L, Yelin EH. The work impact of asthma and rhinitis: findings from a population-based survey. *J Clin Epidemiol* 2001;54:610–618.
16. Vogelzang PF, van der Gulden JW, Tielens MJ, Folgering H, van Schayck CP. Health-based selection for asthma, but not for chronic bronchitis, in pig farmers: an evidence-based hypothesis. *Eur Respir J* 1999;13: 187–189.
17. Ostlin P. The ‘health-related selection effect’ on occupational morbidity rates. *Scand J Soc Med* 1989;17:265–270.
18. Dahl E. Social inequality in health: the role of the healthy worker effect. *Soc Sci Med* 1993;36:1077–1086.
19. Checkoway H, Eisen EA. Developments in occupational cohort studies. *Epidemiol Rev* 1998;20:100–111.

20. Copilevitz C, Dykewicz M. Epidemiology of occupational asthma. *Immunol Allergy Clin North Am* 2003;23:155–166.
21. Radon K, Huemmer S, Dressel H, Windstetter D, Weinmayr G, Weiland S, Riu E, Vogelberg C, Leupold W, von Mutius E, *et al*. Do respiratory symptoms predict job choices in teenagers? *Eur Respir J* 2006;27:774–778.
22. Baillargeon J. Characteristics of the healthy worker effect. *Occup Med* 2001;16:359–366.
23. Pearce N, Checkoway H, Kriebel D. Bias in occupational epidemiology studies. *Occup Environ Med* 2007;64:562–568.
24. Kauffmann F, Drouet D, Lellouch J, Brille D. Occupational exposure and 12-year spirometric changes among Paris area workers. *Br J Ind Med* 1982;39:221–232.
25. McMichael AJ. Standardized mortality ratios and the “healthy worker effect”: scratching beneath the surface. *J Occup Med* 1976;18:165–168.
26. Lea CS, Hertz-Picciotto I, Andersen A, Chang-Claude J, Olsen JH, Pesatori AC, Teppo L, Westerholm P, Winter PD, Boffetta P. Gender differences in the healthy worker effect among synthetic vitreous fiber workers. *Am J Epidemiol* 1999;150:1099–1106.
27. Marabini A, Dimich-Ward H, Kwan SY, Kennedy SM, Waxler-Morrison N, Chan-Yeung M. Clinical and socioeconomic features of subjects with red cedar asthma: a follow-up study. *Chest* 1993;104:821–824.
28. Siracusa A, Kennedy SM, DyBuncio A, Lin FJ, Marabini A, Chan-Yeung M. Prevalence and predictors of asthma in working groups in British Columbia. *Am J Ind Med* 1995;28:411–423.
29. Reijula K, Haahtela T, Klaukka T, Rantanen J. Incidence of occupational asthma and persistent asthma in young adults has increased in Finland. *Chest* 1996;110:58–61.
30. Arif AA, Whitehead LW, Delclos GL, Tortolero SR, Lee ES. Prevalence and risk factors of work related asthma by industry among United States workers: data from the Third National Health and Nutrition Examination Survey (1988–94). *Occup Environ Med* 2002;59:505–511.
31. Eisen EA, Holcroft CA, Greaves IA, Wegman DH, Woskie SR, Monson RR. A strategy to reduce healthy worker effect in a cross-sectional study of asthma and metalworking fluids. *Am J Ind Med* 1997;31:671–677.
32. Ernst P, Dales RE, Nunes F, Becklake MR. Relation of airway responsiveness to duration of work in a dusty environment. *Thorax* 1989;44:116–120.
33. Zock JP, Heederik D, Doekes G. Evaluation of chronic respiratory effects in the potato processing industry: indications of a healthy worker effect? *Occup Environ Med* 1998;55:823–827.
34. Drexler H, Schaller KH, Nielsen J, Weber A, Weihrauch M, Welinder H, Skerfving S. Efficacy of measures of hygiene in workers sensitised to acid anhydrides and the influence of selection bias on the results. *Occup Environ Med* 1999;56:202–205.
35. Kivity S, Shochat Z, Bressler R, Wiener M, Lerman Y. The characteristics of bronchial asthma among a young adult population. *Chest* 1995;108:24–27.
36. Blanc PD, Jones M, Besson C, Katz P, Yelin E. Work disability among adults with asthma. *Chest* 1993;104:1371–1377.
37. Henneberger PK, Deprez RD, Asdigian N, Oliver LC, Derk S, Goe SK. Workplace exacerbation of asthma symptoms: findings from a population-based study in Maine. *Arch Environ Health* 2003;58:781–788.
38. Steenland K, Stayner L. The importance of employment status in occupational cohort mortality studies. *Epidemiology* 1991;2:418–423.
39. Redlich CA, Stowe MH, Wisniewski AV, Eisen EA, Karol MH, Lemus R, Holm CT, Chung JS, Sparer J, Liu Y, *et al*. Subclinical immunologic and physiologic responses in hexamethylene diisocyanate-exposed auto body shop workers. *Am J Ind Med* 2001;39:587–597.
40. Redlich CA, Stowe MH, Coren BA, Wisniewski AV, Holm CT, Cullen MR. Diisocyanate-exposed auto body shop workers: a one-year follow-up. *Am J Ind Med* 2002;42:511–518.
41. Robins JM, Hernan MA, Brumback B. Marginal structural models and causal inference in epidemiology. *Epidemiology* 2000;11:550–560.
42. Hernan MA, Brumback B, Robins JM. Marginal structural models to estimate the causal effect of zidovudine on the survival of HIV-positive men. *Epidemiology* 2000;11:561–570.
43. Greaves IA, Eisen EA, Smith TJ, Pothier LJ, Kriebel D, Woskie SR, Kennedy SM, Shalat S, Monson RR. Respiratory health of automobile workers exposed to metal-working fluid aerosols: respiratory symptoms. *Am J Ind Med* 1997;32:450–459.
44. Blanc PD, Eisner MD, Israel L, Yelin EH. The association between occupation and asthma in general medical practice. *Chest* 1999;115:1259–1264.
45. Toren K, Balder B, Brisman J, Lindholm N, Lowhagen O, Palmqvist M, Tunsater A. The risk of asthma in relation to occupational exposures: a case-control study from a Swedish city. *Eur Respir J* 1999;13:496–501.
46. Karjalainen A, Kurppa K, Martikainen R, Klaukka T, Karjalainen J. Work is related to a substantial portion of adult-onset asthma incidence in the Finnish population. *Am J Respir Crit Care Med* 2001;164:565–568.
47. Le Moual N, Kennedy SM, Kauffmann F. Occupational exposures and asthma in 14,000 adults from the general population. *Am J Epidemiol* 2004;160:1108–1116.
48. Rosenman KD, Reilly MJ, Kalinowski DJ. A state-based surveillance system for work-related asthma. *J Occup Environ Med* 1997;39:415–425.
49. Kennedy SM, Le Moual N, Choudat D, Kauffmann F. Development of an asthma specific job exposure matrix and its application in the epidemiological study of genetics and environment in asthma (EGEA). *Occup Environ Med* 2000;57:635–641.
50. Le Moual N, Siroux V, Pin I, Kaufmann F, Kennedy SM, *for the Epidemiological Study on the Genetics and Environment of Asthma*. Asthma severity and exposure to occupational asthmogens. *Am J Respir Crit Care Med* 2005;172:440–445.
51. Becklake MR, Laloo U. The ‘healthy smoker’: a phenomenon of health selection? *Respiration* 1990;57:137–144.
52. Dosman JA, McDuffie HH, Pahwa P. Atopic status as a factor in job decision making in grain workers. *J Occup Med* 1991;33:1007–1010.
53. Monson RR. Observations on the healthy worker effect. *J Occup Med* 1986;28:425–433.