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Methodological Issues Regarding Confounding and Exposure Misclassification in Epidemiological Studies of Occupational Exposures

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Background *Confounding and exposure misclassification are issues that concern epidemiologists because of their potential to bias results of studies and complicate interpretations. In occupational epidemiology both are routinely raised to argue that an observed result is either a false positive or a false negative finding. Although it is important to consider the potential for limitations of epidemiologic investigations, judgment regarding their importance should be based on their actual likelihood of occurrence.*

Methods *This paper is based on our experience in epidemiologic analyses and a brief review of the literature regarding confounding and exposure misclassification.*

Results *Examples of substantial confounding are rare in occupational epidemiology. In fact, even for studies of occupational exposures and lung cancer, tobacco-adjusted relative risks rarely differ appreciably from the unadjusted estimates. This is surprising because it seems the perfect situation for confounding to occur. Yet, despite the lack of evidence that confounding is a common problem, nearly every epidemiologic paper includes a lengthy discussion on uncontrolled or residual confounding. On the other hand, exposure misclassification probably occurs in all studies. The only question is, how much? The direction and magnitude of nondifferential exposure misclassification (the type most likely to occur in cohort studies) on estimates of relative risks can be largely predicted given knowledge on the degree of misclassification, that is, relatively small amounts of misclassification can bias relative risks substantially towards the null. The literature, however, is full of discussions implying that misclassification of exposure is an explanation for a positive finding.*

Conclusions *These comments are not to suggest that all potential limitations for epidemiologic studies should not be considered and evaluated. We do believe, however, that the likelihood of occurrence and the direction and magnitude of the effect should be more carefully and realistically considered when making judgments about study design or data interpretation.* Am. J. Ind. Med. 50:199–207, 2007. © *2006 Wiley-Liss, Inc.*

KEY WORDS: confounding; exposure misclassification; methods; occupational epidemiology

INTRODUCTION

The potential limitations of observational epidemiologic studies are well described in textbooks on epidemiology. These limitations include confounding, selection bias, information bias, and lack of validity and precision of exposure, and disease determinations. Concerns over these

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limitations are also raised and discussed in most epidemiologic papers. A critical assessment of the strengths and weaknesses of all scientific studies is a crucial component of the scientific method and this process serves to identify false leads, to consider alternative explanations, and to improve study designs. In occupational epidemiology, two limitations that receive considerable attention are confounding and exposure misclassification. Theoretical issues regarding these concepts have been well thought out, can be found in most epidemiologic texts [e.g., Breslow and Day, 1980; Checkoway et al., 2004], and are taught in all epidemiology training programs. We worry, however, that many ''potential'' limitations in epidemiology, particularly confounding and exposure misclassification, have assumed an aura of ''actual'' limitations, where it is not necessary to provide any evidence that the proposed limitation is present. Simply the mention of the possibility of a theoretical limitation is often sufficient to discount the study findings. In the field of occupational epidemiology, it seems that we are especially prone to react in this way on issues that are complex, contentious and hotly debated. These are, of course, the situations where we should demand data, not just opinions. Perhaps we should follow the proposition of Levitt and Dubner [2005] that ''conventional wisdom is often wrong'' and that a hypothesis of bias requires direct evidence to corroborate or refute, just like a hypothesis for a causal relationship.

We emphasize that we are not proposing that potential limitations be ignored. It is important to consider the possible impact of confounding and exposure misclassification on study results. We are concerned, however, that as a discipline, our assessment of the likelihood and impact of these two factors on study findings is unbalanced and this may lead to invalid conclusions, poor decision-making, and faulty public policy. This is clearly a scientific issue, but could also be construed as an ethical issue. Although interpretation of data is not usually recognized as an ethical issue, the American College of Epidemiology Ethics Guidelines identify ''making appropriate interpretations from the data analysis'' as one the criteria in the section on ''Adhering to the highest scientific standards'' [American College of Epidemiology, 2000].

CONFOUNDING

Confounding occurs when a factor is associated with the outcome in the absence of the exposure of interest and also with the exposure of interest. For confounding to occur, the factor must be a risk factor for the outcome and also correlated with the exposure of interest [Checkoway et al., 2004]. What may not be as well appreciated is that for confounders to have much of an impact, both associations (i.e., risk factor for the disease and correlation with the exposure of interest) must be strong [Breslow and Day, 1980]. If this is not the case, the impact of confounding cannot be large. Situations fulfilling these requirements are not common. Despite these rather stringent requirements, we find that many scientific discussions about potential confounding seem to assume that it is common and its impact is sizable. Typically the potential for confounding is hypothesized because some putative risk factor for the outcome of interest, or because some factor thought to be correlated with the exposure of interest has not been addressed in the study design or in the analyses. For example, in evaluating a study of a specific pesticide and lung cancer risk, suspected or established lung carcinogens (with no evidence of a linkage with the pesticide of interest), or other exposures that may coincide with the pesticide of interest (with no indication that they cause lung cancer) may be suggested as possible confounders. In such discussions, it is unusual for both associations to be considered and even rarer for the magnitude of these associations to be evaluated and for supportive data to be provided.

In occupational epidemiology, tobacco or other occupational exposures are commonly raised as potential confounders, particularly with retrospective cohort studies, since these studies often lack information on these factors. However, even without direct information on their occurrence or magnitude in the population under study, the possible impact of such confounding can be estimated.

For example, consider tobacco use as a confounder. Axelson [1978] made an extremely important contribution to this issue when he demonstrated that confounding from tobacco use in occupational studies of lung cancer was unlikely to entirely explain relative risks greater than 1.6. So, even without information on tobacco use, the Axelson approach [1978] could be used to set boundaries regarding the likely impact of smoking confounding. This approach was further evaluated and extended to additive models by Gail et al. [1988]. Using these approaches, the occurrence and likely magnitude of confounding by tobacco can be reasonably estimated because we have a considerable amount of information on relative risks from tobacco use for many diseases, as well as information on tobacco use by various occupations or exposures [Brackbill et al., 1988; Stellman et al., 1988]. With this information, it is relatively easy to estimate the potential impact of confounding by smoking, as suggested by Axelson [1978], thus, negating the need for pure speculation. Kriebel et al. [2004] extended this technique of indirect adjustment in a quantitative evaluation of the possible effects of confounding by tobacco and alcohol use in occupational studies. They concluded that changes of greater than 20% were unlikely.

The potential for confounding by tobacco can also be evaluated by assessing the correlation between smoking and specific occupational exposures. This may not always be possible because the necessary information is often not available. However, Siemiatycki et al. [1988b] evaluated the

relationship between level of exposure to 10 common occupational exposures (sulfur dioxide, welding fumes, engine emissions, gasoline, lubricating oil, solvents, paints/varnishes, adhesives, excavation dust, and wood dust) and tobacco use using data from a case-control study in Montreal. They found no correlation between occupational exposure indices for any of these substances and smoking history. Of course, tobacco use could be associated with other occupational exposures, but these data suggest that a strong association between smoking and specific exposures is unlikely.

Another approach to assess the magnitude and importance of confounding is to examine the impact of adjustment for possible confounders on estimates of relative risks. It has been our experience from numerous analyses for many potential confounders in our own studies that, just as theory indicates [Checkoway et al., 2004; Breslow and Day, 1980], confounding sufficient to affect interpretations of the data is extremely rare. We have not made a thorough review of the literature on this point for this paper, but we present a few examples. Table I presents odds ratios (ORs) for lung cancer by industry and occupation from a case-control study [Levin

TABLE I. Unadjusted and Adjusted (Age and Smoking) Odds Ratios for Lung Cancer by Occupation/Industry [From Levin et al., 1988]

Occupation/industry	Number cases/controls	Unadjusted OR	OR adjusted for age and smoking
Industry			
Agriculture, forestry, fishing	63/47	1.4	1.4
Food manufacturing	28/31	0.9	0.9
Textile	89/128	0.7	0.7
Sewing	34/30	1.2	1.3
Furniture	16/10	1.7	1.3
Chemical	34/25	1.4	1.7
Pharmaceuticals	12/10	1.3	1.2
Rubber and plastic	15/18	0.9	1.0
Metallurgical	84/73	1.2	1.1
General machinery	135/151	0.9	0.9
Electric equipment	27/33	0.8	0.9
Transportation	45/40	1.2	1.1
Precision machinery	23/19	1.3	1.5
Building construction	73/57	1.4	1.2
Food and beverage	198/225	0.9	1.0
Education, culture, arts	61/57	1.1	1.2
Scientific research	14/13	1.1	1.0
State organizations	93/92	1.1	1.0
Occupation			
Professionals/technicians	150/163	0.9	1.1
Service workers	189/172	1.2	1.2
Agricultural workers	54/37	1.6	1.6
Metal smelting	675/57	1.2	1.1
Chemical workers	17/11	1.6	1.4
Textile workers	38/53	0.7	0.7
Tanning and furs workers	12/11	1.1	0.9
Tailoring and sewing workers	21/25	0.9	1.0
Food and beverage workers	21/14	1.6	1.6
Metal forgers, tool makers	114/86	1.4	1.4
Machinery assemblers	53/65	0.8	0.9
Electrical equipment installers	19/25	0.8	0.8
Pipefitters, welders	26/30	0.9	0.9
Glass, ceramic workers	12/17	0.7	0.6
Painters	15/10	1.6	1.4
Construction workers	44/30	1.6	1.4
Power equipment operators	27/20	1.4	1.2
Transportation equipment operators	109/104	1.1	1.1

et al., 1988] where both crude and smoking-adjusted ORs were presented. Of the 36 comparisons of unadjusted and adjusted ORs, 26 were identical or differed by only 0.1, seven changed by 0.2, and two changed by 0.3. The results from an analysis of pooled data from several case-control studies of lung cancer in Germany were similar (Table II)[Bruske-Hohlfeld et al., 2000]. After adjusting for smoking and asbestos exposure, the biggest change in the ORs for lung cancer was about 0.3 or more and most ORs hardly changed at all. Similar results were found in a case-control study of lung cancer in Italy [Richiardi et al., 2005]. Likewise, Siemiatycki et al. [1988a] compared 75 smoking adjusted and smoking unadjusted relative risks for lung, bladder and stomach cancer. Only eight comparisons had differences of 20% or greater (seven for lung cancer and one for bladder cancer). Adjustment for smoking in a cohort study where the prevalence of smoking was positively correlated with the estimated level of exposure to acrylonitrile is shown in Table III [Blair et al., 1998]. The prevalence of ever smoking increased from 62% among workers in the lowest exposure

TABLE II. Odds Ratios for Lung Cancer With Different Adjustments (Age; Age, Smoking; and Age, Smoking, Asbestos) by Occupation/Industry [From Bruske-Hohlfeld et al., 2000]

	Number case/controls	Age adjusted OR	Age, smoking adjusted OR	Age, smoking, asbestos adjusted OR
Industry				
Agriculture, forestry, fishing	812/951	1.29	1.30	1.32
Energy and mining	274/440	1.72	1.47	1.44
Chemicals and oil	98/117	1.23	1.19	1.16
Rubber and plastics	43/85	2.04	1.94	1.89
Stone, glass, pottery	165/276	1.80	1.55	1.50
Metal production	574/764	1.45	1.37	1.27
Engine/vehicle building	791/1000	1.40	1.32	1.21
Electrical and sheet metal	499/446	0.89	0.90	0.87
Paper, wood, and printing	362/426	1.24	1.28	1.31
Food and tobacco	232/276	1.23	1.04	1.07
Construction	706/1004	1.63	1.35	1.32
Wholesale trade	475/404	0.83	0.71	0.73
Shipping and storage	318/410	1.37	1.13	1.14
Financing and insurance	119/97	0.79	0.76	0.79
Restaurants and hotels	128/166	1.36	1.04	1.06
Education, health, research	99/156	1.60	1.24	1.27
Occupation				
Farmer, agricultural workers	662/770	1.26	1.29	1.31
Forestry worker, fisherman	125/179	1.52	1.57	1.61
Miner	211/380	1.92	1.64	1.65
Stone cutter and carver	75/96	1.34	1.07	1.04
Chemical processor	104/170	1.69	1.56	1.55
Paper maker, printer	76/71	0.95	0.87	0.89
Cabinet maker	274/314	1.20	1.32	1.36
Metal producer and processor	460/731	1.77	1.49	1.42
Machinery mechanic, plumber	904/983	1.14	1.13	0.99
Electrician	286/246	0.87	0.87	0.82
Textile and leather worker	157/180	1.20	1.13	1.17
Food and beverage processor	218/281	1.35	1.14	1.17
Bricklayer, carpenter	330/498	1.65	1.39	1.33
Plasterer, insulator, upholsterer	108/152	1.43	1.37	1.34
Painter and lacquerer	96/147	1.60	1.39	1.42
Architect, technician, engineer	754/409	0.49	0.61	0.60
Sales worker	565/447	0.76	0.70	0.73
Medical, dental, veterinary worker	83/43	0.50	0.58	0.60
Social worker, teacher, scientist	361/122	0.32	0.39	0.41

TABLE III. Relative Risks for Lung Cancer by Estimated Level of Acrylonitrile Exposure Adjusted for Age, Calendar Time, Gender, and Race and also for Cigarette Use [From Blair et al., 1998]

	Quintile of estimated exposure					
Analysis group	**Lowest**	**2nd**	**3rd**	**4th**	**Highest**	***P* for trend**
% Ever smoked cigarettes	62%	64%	68%	72%	75%	
Full cohort	1.1	1.3	1.2	1.0	1.5	0.65
Selected smoking subcohort, not adjusted for smoking	0.8	1.1	1.0	0.9	1.5	0.70
Smoking subcohort with information on cigarette use, not adjusted for smoking	0.3	0.9	1.0	1.0	1.7	0.80
Smoking subcohort, adjusted for number of cigarettes per day	0.3	0.7	1.1	1.0	1.7	0.96
Full cohort with estimated changes from the smoking subcohort	1.1	1.0	1.1	0.9	1.4	

quintile to 75% in the highest. In this case, smoking was associated with the exposure of interest and we thought that the nonsignificant excess for lung cancer in the highest quintile (relative risk (RR) = 1.5) could be due to confounding. Because lung cancer was the a priori disease of interest, information on tobacco use was obtained from the next-of-kin of all the lung cancer cases and a 10% sample of the cohort on the noncases. Adjustment for smoking did not eliminate the elevated RR in the upper quintile. The RR for lung cancer in the highest quintile of exposure of the smoking subcohort increased from 1.5 to 1.7 without adjustment for tobacco use, but was unchanged when adjusted for smoking. Thus, the smoking–exposure relationship observed was apparently not tight enough to have much of an effect on the acrylonitrile/lung cancer relationship. Similar conclusions have been made in other analyses and surveys evaluating possible confounding by smoking in occupational studies [Blair et al., 1985; Simonato et al., 1988]. Data from studies of well-established occupational carcinogens also indicate that tobacco use does not confound these associations. For example, respiratory cancer is a well-demonstrated consequence of arsenic exposure among smelter workers [Lubin et al., 2000]. Tobacco does not appear to be associated with level of exposure and, consequently, does not confound the arsenic-respiratory cancer relationship [Welch et al., 1982]. Radon exposure among uranium miners has a sizable impact on lung cancer and this relationship is not confounded by smoking [Labbe et al., 1991]. Thus, these findings on well-established carcinogens indicate that confounding by tobacco use in occupational studies of lung cancer is rare and is not likely to be an explanation for positive study findings. We think the fact that tobacco use, which is the major risk factor for lung cancer and which differs by occupation and sometimes by estimated exposure to specific chemicals, rarely confounds disease risks from occupational associations is instructive. If tobacco does not confound lung cancer risks in occupational studies, it is even less likely that more modest risk factors for various diseases and with no known association with the exposure of interest would have a substantial effect.

Potential confounding from other exposures in the workplace is more difficult to evaluate [Blair et al., 1995]. This is because information is seldom available on the correlation between different occupational exposures, although we know that most work places have multiple exposures. What is often available, however, is information regarding the potential for these ''other'' exposures to cause the disease of interest. If experimental and epidemiologic studies do not suggest an association between a potential confounder and the disease, then perhaps we need not be as concerned that these factors function as confounders. Experience from our own studies and the article by Bruske-Hohlfeld et al. [2000] indicates that confounding by other work place exposures is also rare. Similarly, adjustment for asbestos exposure had little effect on the relationship between crystalline silica and lung cancer in diatomaceous earth workers [Checkoway et al., 1997]. Thus, a cursory examination of the literature suggests that confounding from other occupational exposures is not likely to be a common occurrence.

EXPOSURE MISCLASSIFICATION

It is important to note that the definition of exposure and the presence of exposure misclassification is tied to the objectives of the research. For example, if the study goal is to evaluate the association between airborne measurements of radon gas and lung cancer in underground miners, then an exposure assessment based on airborne measurements (if performed appropriately) may not suffer from much misclassification (measurement error would still occur) and the estimates of relative risk are unbiased. In contrast, misclassification is more likely to occur if the goal is to evaluate the risk of lung cancer by delivered dose of radiation to the lung tissue and exposure estimates were based on entirely on airborne measurements.

For etiologic research, a reasonable theoretical construct for exposure is ''delivered dose to the target cell.'' Although desirable, this definition of exposure is largely unachievable. In practice, measured levels or estimates in air, water, dust, or

biologic tissues serve as surrogates for delivered dose. Axelson [1985] noted that assessment for relatively short (hours or days) exposures, for example, accidents or similar events, or constant/life-long exposures can sometimes be relatively easy, but these situations are rare. More typically, exposures over a longer period of time period are of interest. Since occupational exposures vary in intensity over time, it is difficult to create an accurate time-dependent exposure model.

The theoretical underpinnings for exposure misclassification are well developed. Checkoway et al. [2004] describe this as information bias. Exposure misclassification can either be non-differential (the probability or degree of misclassification is the same among diseased and non-diseased subjects), or differential (the probability or degree of misclassification is not the same among the diseased and non-diseased). Non-differential misclassification tends to bias relative risks toward the null for dichotomous exposure classifications. Although it can move estimates of relative risks away from null for some categories in multi-level exposure indices, in the highest exposure category it can only diminish the relative risk [Dosemeci et al., 1990]. Thus, in multi-level exposure analyses, non-differential misclassification tends to disrupt exposure-response trends and diminish our confidence that a causal association exists. In cohort studies, exposure misclassification is typically thought to be nondifferential because exposure assessment is independent from diagnosis of disease. In contrast, differential misclassification of exposure can bias the relative risks toward or away from the null. This type of misclassification is typically thought of as more of a concern in case-control studies because information on exposure is often obtained after diagnosis of disease. It is our impression that clear evidence for differential misclassification in case-control studies is relatively uncommon, but we did not perform a thorough review of the epidemiologic literature on this point. The likely occurrence of nondifferential misclassification of exposure, however, does not insure that the relative risks are underestimated. This is because misclassification of exposure is not the only source of bias and other sources could move the risk estimates away from the null [Jurek et al., 2005]. On the other hand, nondifferential misclassification itself is unlikely to create false positive findings.

It is more difficult to evaluate the impact of exposure misclassification on relative risks in occupational studies than for confounding because of the absence of information on the level of misclassification present. The theoretical impact of exposure misclassification on relative risks, however, can be estimated with information on the validity of exposure measurements/assessments and predicted relative risks [Rothman and Greenland, 1998; Checkoway et al., 2004]. A number of publications have described the theoretical impact of misclassification. They demonstrate that the magnitude of the effect of exposure misclassification on estimates of relative risk varies by the degree of misclassification and prevalence of the exposure. It is clear from these publications that relatively small errors (i.e., 10%–20%) can have sizable effects on relative risks [Copeland et al., 1977; Flegal et al., 1986].

If the desired characterization of exposure in etiologic studies is delivered dose to the target tissue, then no epidemiologic study is free from exposure misclassification. Unfortunately, the difficulty of obtaining true ''gold standard'' measurements means we never precisely know where we stand on the misclassification scale. It is likely, however, that even when basing exposure estimates on environmental or biologic measurements, our estimate of exposure is not likely to be very accurate if ''delivered dose to the target organ'' is the desired construct. Thus, even in the best of circumstances, exposure misclassification is likely to be considerable, and most epidemiologic studies do not possess ''ideal'' exposure measures. Some indication of the accuracy of occupational exposure assessment, however, can be gleaned from reports that compare different methods to assess a particular exposure. The sensitivity and specificity or correlation between two methods of exposure assessment provides some indication of the possible magnitude of misclassification, although it is important to remember that neither is likely to represent a ''gold standard.''

Table IV displays a few selected comparisons of occupational exposure assessments from the literature. The level of agreement in these studies shows Kappa values from ranging from 0.40 to 0.70 and correlations from 0.10 to 0.70. These values are roughly equivalent to the degree of misclassification and indicate that the level of disagreement between different measures of exposure is likely to exceed 30% in most circumstances and maybe as high as 70%. Use of these values as the actual range of misclassification assumes that one of the measures represents the ''gold standard.'' Since they do not, we are unsure of the how well the relationship between these two factors reflects that actual amount of misclassification.

The effect on relative risks from nondifferential misclassification in the 30%, percent range is sobering. Just in terms of relative ranking of subjects, Walker and Blettner [1985] showed that the classification of subjects by an exposure estimate that has a correlation of 0.70 with the true measure results in only 40% of the subjects being placed in the correct quintile of exposure. Even accepting correct placement by quintile as a success, it means that about 60% of the subjects would not be in the correct exposure quintile. Moreover, misclassification of exposure of this magnitude would have a considerable impact on estimates of relative risk. For example, Table V shows the impact of exposure misclassification on relative risks in hypothetical situations with a sensitivity of 0.7, specificity of 0.7 or 1.0, exposure prevalences of 10%, 30%, or 50% and true relative risks of

TABLE IV. Studies Reporting Different Exposure Assessment Techniques

Reference	Type of estimate	Exposure	Agreement
Friesen et al. [2003]	Expert estimate and measurements	Coal tar pitch volatiles	r = 0.42
Benke et al. [1997]	Expert estimate and measurements	Cutting, fluids-welding, fumes, lubricating oils	Kappa = 0.64, Kappa = 0.57, Kappa = 0.42
Ahrens et al. [1993]	JEMs, JEMs + questionnaires	Asbestos, asbestos	Kappa = 0.67, Kappa = 0.40
Baugher [1994]	PK model and measurements	2,4-D	r = 0.65
Steenland et al. [1999]	Expert estimates and serum measurements	2,3,7,8 tetrachloro-dibenzo-p-dioxin	r = 0.70
Stewart et al. [2003]	Deterministic, ratio, and homogeneous group methods with exposure measurements	Acrylonitrile	r = 0.63, r = 0.64, r = 0.66
Nieuwenhaijsen et al. [1995]	Estimates for average, cumulative, peak levels	Allergens	r range from 0.39 to 0.68
Stewart et al. [2000]	Expert estimates	Formaldehyde	r = 0.4 to 0.5

2.0 or 3.0. We chose these sensitivity and specificity values because they are roughly similar to level of exposure misclassification from the studies in Table IV. The amount of downward bias observed in situations displayed here is of such a magnitude that a reasonable interpretation of some of these observed relative risks would be that no association exists, even for a true relative risk of three. The observed relative risks are similar to what we often see in occupational studies, raising the question that we may be missing many occupational hazards because of exposure misclassification. In many, probably most, occupational studies, the sensitivity and specificity of exposure assessment may not reach 70% as assumed here and the level of bias would be even greater than displayed in Table V.

MISCLASSIFICATION OF A CONFOUNDER

Confounding factors can also suffer from misclassification. This is probably a common occurrence. The effects of confounder misclassification have been well discussed by Savitz and Baron [1989]. They make the point that in the presence of confounding, statistical adjustment is likely to be incomplete because of misclassification of the confounder and that the amount of confounding remaining is likely to be proportional to the amount removed in the adjustment process. Thus, misclassification of actual confounders would result in a general under assessment of the amount of confounding. Concern about residual confounding would be confined to situations where a meaningful difference is found between the adjusted and unadjusted point estimates, unless exposure assessment for the confounder is completely random.

TABLE V. Observed Relative Risks Based on Sensitivity, Specificity, Exposure Prevalence and True Relative Risks

True relative risk and prevalence of exposure	Sensitivity = 0.7; specificity = 1.0	Sensitivity = 0.7; specificity = 0.7
True relative risk = 2.0		
Exposure prevalence = 10%	1.94 (0.808)	1.15 (0.194)
Exposure prevalence = 30%	1.80 (0.760)	1.30 (0.359)
Exposure prevalence = 50%	1.63 (0.700)	1.31 (0.400)
True relative risk = 3.0		
Exposure prevalence = 10%	2.82 (0.808)	1.29 (0.194)
Exposure prevalence = 30%	2.44 (0.766)	1.53 (0.359)
Exposure prevalence = 50%	2.05 (0.700)	1.50 (0.400)

Kappas for the corresponding sensitivity, specificity, and exposure prevalence are in parentheses.

CONCLUSIONS

We believe of the two of the major methodologic issues raised in epidemiologic studies of occupational exposures, that is, confounding and exposure misclassification, the latter is of far greater concern. It is rare to find substantial confounding in occupational studies (or in other epidemiologic studies for that matter), even by risk factors that are strongly related to the outcome of interest. On the other hand, exposure misclassification probably occurs in nearly every epidemiologic study. For nondifferential misclassification, the type of misclassification most likely in cohort studies, the direction of the bias is largely predictable, that is, a bias of relative risks toward the null. In addition, the magnitude from relatively small amounts of misclassification can be sufficient to lead to an interpretation of no effect. Thus, interpretation of epidemiologic data and evaluations of epidemiologic studies should be more concerned about exposure assessment than confounding.

We find this is not usually the case. Extensive discussion of potential for confounding from specific, and sometimes unspecified, factors occurs routinely. Confounding is often raised as an explanation for positive findings without providing any information that the very specific conditions

required for it to occur actually do. On the other hand, discussions of exposure misclassification, if they occur at all, often imply that it may have created a false positive finding, even for cohort studies where nondifferential misclassification is likely to have the opposite effect. We think the relative attention paid to potential biases from confounding and exposure misclassification is unbalanced. To provide sound evaluations of epidemiology data, comments on confounding and exposure misclassification need to indicate the probability of occurrence, and magnitude and direction of possible effects to make sound scientific judgments and public policy decisions.

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REFERENCES

Ahrens W, Jockel KH, Brochard P, Bolmaudorff U, Grossgarten K, Iwatsubo Y, Orlowski E, Pohlabeln H, Berrino F. 1993. Retrospective assessment of asbestos exposure. 1. Case-control analysis in a study of lung cancer efficientcy of job-specific questionnaires and job exposure matrices. Int J Epidemiol 22:s83–s95.

American College of Epidemiology. 2000. American College of Epidemiology Ethics Guidelines. Ann Epidemiol 10:487–497.

Axelson O. 1978. Aspects on confounding in occupational health epidemiology. Scand J Work Environ Health 10:325–326.

Axelson O. 1985. Dealing with the exposure variable in occupational and environmental epidemiology. Scand J Soc Med 18: 147–152.

Baugher DG. 1994. Validation of a pharmacokinetic model to predict exposure of ground boom mixer-loader-applicators to chlorophenoxyacetic acid herbicides—Comparison to conventional approaches. ACS Symposium Ser 542:214–230.

Benke G, Sim M, Forbes A, Salzberg M. 1997. Retrospective assessment of occupational exposure to chemicals in community-cased studies; validity and repeatability of industrial hygiene panel ratings. Int J Epidemiol 26:635–642.

Blair A, Hoar S, Walrath J. 1985. Comparison of crude and smoking-adjusted standardized mortality rates. J Occup Med 27:881–884.

Blair A, Stewart WF, Stewart PA, Sandler DP, Axelson O, Vineis P, Checkoway H, Savitz D, Pearce N, Rice C. 1995. A philosophy for dealing with hypothesized uncontrolled confounding in epidemiological investigations. Med Lav 86:106–110.

Blair A, Stewart PA, Pottern L, Zey JN, Bloom TF, Miller B, Ward E, Lubin J. 1998. Mortality of industrial workers exposed to acrylonitrile. Scand J Work Environ Health 24(Suppl 2):25–41.

Brackbill R, Frazier T, Shilling S. 1988. Smoking characteristics of US workers, 1978–1980. Am J Ind Med 13(1):5–42.

Breslow NE, Day NE. 1980. Statistical methods in cancer research, Vol. 1. In: The analysis of case-control studies. Lyon: IARC Sci Publ No. 338p.

Bruske-Hohlfeld I, Mohner M, Pohlabein H, Ahrens W, Bolm-Audorff U, Kreienbrock L, Kreuzer M, Jahn I, Wichmann H-E, Jockel K-H. 2000. Occupational lung cancer risk in Germany: Results from a pooled case-control study. Am J Epid 151:384–395.

Checkoway H, Heyer NJ, Seixas NS, Welp EA, Demers PA, Hughes JM, Weill H. 1997. Dose-response associations of silica and nonmalignant respiratory disease and lung cancer mortality in the diatomeous earth industry. Am J Epidemiol 145(8):680–688.

Checkoway H, Pearce N, Kriebel D. 2004. Research methods in occupational epidemiology. New York: Oxford University Press. 393p.

Copeland KT, Checkoway H, McMichael AJ, Holbrook RH. 1977. Bias due to misclassification in the estimation of relative risk. Am J Epidemiol 105:488–493.

Dosemeci M, Wacholder S, Lubin JH. 1990. Does nondifferential misclassification of exposure always bias the true effect toward the null? Am J Epidemiol 132:746–748.

Friesen MC, Demers PA, Spinelli JJ, Le ND. 2003. Validation of a semi-quantitative job exposure matrix at a Soderberg aluminum smelter. Ann Occup Hyg 47:477–484.

Gail MH, Wacholder S, Lubin JH. 1988. Indirect corrections for confounding under multiplicative and additive risk models. Am J Ind Med 13:119–130.

Jurek AM, Greenland S, Maldonado G, Church TR. 2005. Proper interpretation of non-differential misclassification effects: Expectations vs. observations. Int J Epid 34:680–687.

Kriebel D, Zeka A, Eisen EA, Wegman DH. 2004. Quantitative evaluation of the effects of uncontrolled confounding by alcohol and tobacco in occupational cancer studies. Int J Epidemiol 13:1–6.

Labbe KA, Howe GR, Burch JD, Miller AB, Abbatt J, Band P, Choi W, Du J, Feather J, Gallager R, Hill G, Mathews V. 1991. Radon exposure, cigarette-smoking, and other mining experience in the Beaverlodge uranium miners cohort. Health Phys 60:489–495.

Levin L, Zheng W, Blot WJ, Gao Y-T, Fraumeni JF, Jr. 1988. Occupation and lung cancer in Shanghai: A case-control study. Brit J Ind Med 45:450–458.

Levitt SD, Dubner SJ. 2005. Freakonomics: A rogue economist explores the hidden side of everything. New York: HarperCollins Books. 242p.

Lubin JH, Pottern LM, Stone BJ, Fraumeni JF, Jr. 2000. Respiratory cancer in a cohort of copper smelter workers: Results from more than 50 years of follow-up. Am J Epid 151:554–565.

Nieuwenhaijsen MJ, Lowson D, Venables KM, Newman Taylor AJ. 1995. Correlation between different measures of exposure in a cohort of bakery workers and flour millers. Ann Occup Hy 39:291–298.

Richiardi L, Forastiere F, Boffetta P, Simonato L, Merletti F. 2005. Effect of different approaches to treatment of smoking as a potential confounder in a case-control study on occupational exposures. Occup Environ Med 62(2):101–104.

Rothman JK, Greenland S. 1998. Modern epidemiology. 2nd edn. Philadelphia: Lippincott-Raven.

Savitz D, Baron AE. 1989. Estimating and correcting for confounder misclassification. Am J Epid 129:1062–1071.

Siemiatycki J, Wacholder S, Dewar R, Cardis E, Greenwood C, Richardson L. 1988a. Degree of confounding bias related to smoking, ethnic-group, and socioeconomic-status in estimates of the associations between occupation and cancer. J Occup Environ Med 30: 617–625.

Siemiatycki J, Wacholder S, Dewar R, Wald L, Begin D, Richardson L, Rosenman K, Gerin M. 1988b. Smoking and degree of occupational exposures: Are internal analyses in cohort studies

likely to be confounded by smoking status? Am J Ind Med 13:59–70.

Simonato L, Vineis P, Fletcher AC. 1988. Extimates of the proportion of lung cancer attributable to occupational exposure. Carcinogenesis 9:1159–1165.

Steenland K, Piacitelli L, Deddens J, Fingerhut M, Chang LI. 1999. Cancer, heart disease, and diabetes in workers exposed to 2,3,7,8-tetrachlorodibenzo-p-dioxin. JNCI 91:779–786.

Stellman SD, Boffetta P, Garfinkel L. 1988. Smoking habits of 800,000 American men and women in relation to their occupation. Am J Ind Med 13(1):43–58.

Stewart PA, Carel R, Schairer C, Blair A. 2000. Comparison of industrial hygienists' exposure evaluations for an epidemiologic study. Scand J Work Environ Health 26:44–51.

Stewart PA, Lees PSJ, Correa A, Breysse P, Gail M, Gruabard BI. 2003. Evaluation of three retrospective exposure assessment methods. Ann Occup Hyg 47:399–411.

Walker AM, Blettner M. 1985. Comparing imperfect measures of exposure. Am J Epid 121:783–790.

Welch K, Higgins I, Oh M, Burchfiel C. 1982. Arsenic exposure, smoking, and respiratory cancer in copper smelter workers. Arch Environ Health 37:325–335.