Letter to the editor

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Letter to the Editor

Aspects on confounding in occupational health epidemiology

In occupational health epidemiology, general risk indicators of disease, such as smoking, misuse of alcohol, etc., often attract considerable interest as an alternative or contributing explanation for excess morbidity associated with industrial exposure. Thus, when, e.g., lung cancer is discussed as possibly having an occupational origin, smoking habits might be suggested to cause the excess morbidity rather than a certain work environment. Arguments for this view obviously derive from the well-known connection between smoking and lung cancer and from the fact that most of the cases in a study are usually found to be smokers. The question is, however, if the exposed population, as the deliverer of cases, might comprise a higher percentage of smokers than the comparison population, the provider of the reference level of the morbidity at issue; i.e., if smoking might be related to exposure, in addition to being a risk indicator of the disease, and therefore constitute a confounding factor (12).

In view of the character of a confounding factor as related to both exposure and disease, it is rather obvious that such risk indicators as, say, smoking or alcohol misuse do not usually have any strong confounding properties, as they are not more closely related to a specific occupational exposure. Exceptionally some degree of association might occur, and it is therefore desirable to control such factors whenever possible, i.e., when not practically impossible or unduly expensive, although the influence on the risk estimate would be limited. Moreover, the control of these factors would not necessarily tend to weaken the association between exposure and outcome, but it might sometimes result in some strengthening of the effect under study, namely, if the confounding effect happens to be negative (or masking). Thus, a stable labor force, accumulating long-time exposure to a certain agent or process, would rather tend to be low grade users of alcohol, and particular occupational groups might be found to smoke somewhat less than the average (or reference) population, as did painters in a region of Sweden (5); i.e., smoking is then negatively related to the occupational exposure.

EVALUATION OF CONFOUNDING

In the prestudy situation, judgements about possible confounding factors have to be based on general knowledge and experience from similar studies. A quantitative evaluation of the strength of various confounding factors, accounted for in the study, might be obtained through the calculation of the confounding risk ratio, which is the ratio of the crude risk ratio and the standard morbidity ratio (SMR) (11).

However, the discussions about a particular study do not usually bring up those confounding effects as accounted for, but rather focus on the possibility of remaining, uncontrolled confounding. Also concern in this respect should be referred to a quantitative elucidation, however, which might be based on the following relation:

$$I = I_{CF}P_{CF} + I_0(1 - P_{CF}), \quad (1)$$

where I is the overall incidence of a certain illness in a given population, I_{CF} is the incidence as caused by the confounding factor (being a risk indicator for the disease), P_{CF} is the proportion of the population

with the factor in question, and I_0 is the incidence among those without the risk indicator [cf. MacMahon and Pugh (8), p. 274].

If the effect of any potentially confounding factor is known in terms of a risk ratio, R, the formula might be written

$$I = RI_0P_{CF} + I_0(1 - P_{CF}). \quad (2)$$

This model can be extended to comprise several terms, e.g., in respect to various levels of the confounder in question or with regard to different confounders.

In an attempt to evaluate the possible confounding effect of smoking with regard to lung cancer, one might first consider a reference population as comprising, say, 50 % nonsmokers, 40 % moderate smokers with a 10-fold risk of lung cancer, and 10 % heavy smokers with a 20-fold increased risk. Since the reference risk is defined as unity, one gets

$$I = 0.5\,I_0 + (0.4)\,(10)\,I_0 + (0.1)\,(20)\,I_0 \quad (3)$$

and thus $I_0 = 0.1538\,I$.

With the utilization of this model and value on I_0 and the consideration of populations with various compositions of nonsmokers, smokers and heavy smokers, table 1 might be constructed. It is evident that the confounding effect, as caused by deviating smoking habits, can usually be expected to be rather weak in relation to an overmorbidity of, say, 5—10 times the normal, as is often found in occupational health epidemiology. Similarly, confounding in the context of cardiovascular disease as related to smoking will be still weaker since the overmorbidity due to smoking is only on the order of about three times the normal.

The confounding factors discussed so far are of a general type and more or less common to all fields of epidemiology. They tend to be considered from a qualitative point of view only and sometimes attract more concern in occupational health than is always necessary with regard to their confounding effects. However, these types of risk indicators are of greater interest as modifiers of the effect (12) exerted by industrial exposures. Thus, lung cancers tend to appear among smokers also in the presence of a causal industrial risk indicator. The deleterious effect of the combined exposure to asbestos and cigarette smoking might be recalled as an example of this mechanism.

Table 1. Estimated crude rate ratios in relation to fraction of smokers in various hypothetical populations. Two different risk levels are assumed for smokers, i.e., 10 times and 20 times that of nonsmokers for "moderate" and "heavy" smokers, respectively (2, 4).

Population fraction (%)			Rate ratio
Nonsmokers (1x)	Moderate smokers (10x)	Heavy smokers (20x)	
100	—	—	0.15
80	20	—	0.43
70	30	—	0.57
60	35	5	0.78
50[a]	40[a]	10[a]	1.00[a]
40	45	15	1.22
30	50	20	1.43
20	55	25	1.65
10	60	30	1.86
—	65	35	2.08
—	25	75	2.69
—	—	100	3.08

[a] Reference population (similar to the general population in countries like Sweden). Smoking habits in various industrial populations are rarely diverging outside the broken lines.

INTERCONFOUNDING EXPOSURE

There is also another aspect to be considered in the context of occupational health studies, namely, confounding as inherent in combined exposures. For example, exposure to volatile anesthetics might cause miscarriages and birth defects (7) and, as judged from recent experience, there also seems to be a risk of birth defects due to the use of hexachlorophene soap (3). It is obvious that personnel exposed to anesthetics might also have used hexachlorophene soap for surgical washing, i.e., the exposures to anesthetics and hexachlorophene soap are both related to surgery, and both exposure factors might cause the same effect. Thus the use of hexachlorophene soap becomes a confounding factor in the study of birth defects among the children of hospital personnel as due to exposure to anesthetics. With a reference population without exposure to any of these risk indicators, the aspect of confounding apparently changes to one of effect-modification. Thereby the effect of these two factors might be distinguished through categorization with regard to mixed and pure exposures. This approach is commonplace in occupational health studies, although little

Table 2. A case-referent study on tumor incidence (WHO 140—205) during 1957—72 concerning Swedish railroad workers with > 45 days of total (combined) herbicide exposure.[a]

Case no.	Case	Referents			
Phenoxy acids (2, 4-D; 2, 4, 5-T)[b]					
098	—	II	II	—	—
079	I	III	—	II	—
257	—	—	I	II	—
135	—	I	—	—	—
127	II	—	—	—	III
354	—	—	—	III	—
014	—	—	—	III	—
256	—	—	I	—	II
009	II	II	II	II	—
309	II	—	—	II	—
317	II	—	—	—	I
163	—	—	I	—	II
268	III	II	II	—	II
172	II	—	—	—	—
266	III	II	III	II	—
334	II	III	II	—	I
Amitrol[c]					
098	I	II	II	—	III
079	I	III	I	—	III
257	III	I	II	—	III
135	III	—	II	I	—
127	—	—	—	I	—
354	II	—	—	—	—
014	III	—	II	III	I
256	III	III	—	III	—
009	II	—	—	—	III
309	II	III	II	—	III
317	—	I	—	I	—
163	I	—	I	II	—
263	—	—	—	III	—
172	—	—	—	—	—
266	III	—	—	—	II
334	II	—	—	II	—

[a] Amount of exposure (≥ 1 day I; > 45 days II; > 90 days III) at date of case's last exposure, age-matched (within 1.5 years).
[b] ≥ 1 day $p < 0.28$ (one-tailed); relative risk (rate ratio) = 1.6.
[c] ≥ 1 day $p < 0.025$ (one-tailed); relative risk (rate ratio) = 4.6.

Table 3. Case-referent data, as derived from table 2, showing a masking, interconfounding effect from various herbicides with regard to tumor incidence.

Cases/referents	Exposure[a]				
		Phenoxy acids			
	Amitrol	—	I	II—III	I—III
Cases	—	0	0	4	4
Referents		14	4	18	22
Cases	I—III	7	1	4	5
Referents		22	2	4	6
Cases		7	1	8	9
Referents		36	6	22	28
Crude rate ratio		(1)	0.9	1.9	1.6
Standard morbidity ratio		(1)	1.6	6.3	4.7

[a] I = ≥ 1 day of exposure, II = > 45 days of exposure; III = > 90 days of exposure.
χ^2 (1) [Mantel-Haenszel (9); unexposed vs. exposed] = 3.76.

effort usually is made to distinguish between different interconfounding exposures. Instead, these are rather blocked by consideration of only the occupational title as the exposure.

To further illustrate the interconfounding effects from two various occupational exposures, a study concerning cancer effects in relation to herbicide exposure (1) might be utilized. Thus, one of several herbicides (amitrol) was thought to be the main cause of the overmorbidity as found in the study. A case-referent approach was applied within the cohort to get some further elucidation of the influence from smoking and for the evaluation of dose-response relationships. The data in table 2 are taken from this study. Matching for age was applied but was not particularly relevant, since the rate ratio did not change very much when the tuplets were dissolved. Thus, the rate ratio decreased from 4.6 to 3.9 in respect to amitrol exposure and increased from 1.6 to 1.7 for exposure to phenoxy acids, i.e., age had a weak positive confounding effect with regard to exposure to phenoxy acids and a masking or negative confounding effect in view of amitrol exposure.

However, dissolving the tuplets and combining these two tables, one obtains table 3 which reveals a possible and previously masked tumor inducing effect also from phenoxy acids (a corresponding table might be constructed for amitrol exposure and it might show a further increase in the SMR also in this respect).

SUMMARIZING SOME EXPERIENCES ON CONFOUNDING

From these examples one might conclude that there are qualitative as well as quantitative aspects of confounding in occupational health studies, and the concerns about confounding should not only be focused on the possible effects from such general risk indicators as smoking, alcohol misuse, etc., but should also consider combined occupational exposures. Then, the presumed confounding effect from general risk indicators might be found to be rather weak, absent or even masking, rather than exaggerating the effect of a particular industrial exposure. Interconfounding effects from combined exposures might sometimes obtain, and turn out to act in, a surprising direction.

Moreover, an a posteriori evaluation is desirable with regard to the measures undertaken to control confounding in a particular study. A good example in this respect can be found in a study of mortality from coronary heart disease among workers exposed to carbon disulfide (6). Thus age, birth district, and similarity of work

were assumed to be confounding factors and matched for, but later it was shown that this matching procedure was rather irrelevant. Others seem to have had similar experiences with regard to age (10). However, in the great majority of studies no evaluations at all have been made, although highly desirable as contributing to the conceptualization of the structure and strength of confounding in occupational health epidemiology.

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