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Occupational mortality studies

Principles of validity

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WANG J-D, MIETTINEN OS. Occupational mortality studies: Principles of validity. *Scand j work environ health* 8 (1982) 153—158. Two common practices of occupational mortality studies have no model in experimentation: (a) the use of the "general population" as a reference population and (b) the use of the total number of deaths as a surrogate for the population-time of follow-up. The former tends not to secure validity in terms of (i) comparability of effects, ie, identity of the extraneous effects of the compared experiences; (ii) comparability of populations, ie, absence of intractable confounding; and (iii) comparability of information, ie, identity of the certification of deaths from the illness of interest for the contrasted populations. The use of a carefully selected, occupational reference population is necessary for all three types of comparability. When deaths from other (auxiliary) diseases are used to estimate the relative magnitudes of the compared populations, careful selectivity is again called for. With respect to auxiliary causes of death, also, the compared occupational populations must satisfy all three aspects of comparability, with the added requirement that the exposure under study have no effect. The "healthy worker effect" is the result of failure to use comparable reference populations in occupational mortality studies.

Key terms: epidemiologic methods, statistics.

In occupational mortality studies it is commonplace to compare the mortality of a population in a particular occupation with that of the "general population." The former is generally found to be lower than the latter, and the difference is referred to as the "healthy worker effect" (16). If therapeutic research were conducted in an analogous manner, treated patients would be compared with the "general population" for any criterion of outcome. Experience would show that the treated group usually has a worse outcome than the reference population, and the difference might be referred to as the "sick patient effect."

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When the size of the occupational population under study is unknown, it is customary to compare the proportions of deaths of interest among all deaths (26). For this practice the counterpart in clinical trials would be the comparison of treatment groups in terms of the proportion of events of interest among all events within the treatment groups. It is evident that these common practices in occupational mortality research are far removed from the experimental paradigm advocated for nonexperimental research by AB Hill (12), among others.

In this paper we have attempted to delineate the implications of the experimental model for validity in occupational mortality studies. In particular, our concern is to put forth some key principles of validity for forming population contrast, as well as for coping with the common lack of direct "denominator data." We have also discussed the "healthy worker effect" as a manifestation of the violation

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of one of the principles of validity that we advocate.

Object of study

Meaningful discussion of validity in occupational mortality (or any other type of) research presupposes keen appreciation of the nature of the object of study. There is little scientific point in knowing the mortality from any disease Y in any occupation X in an absolute sense. Nor is there any intrinsic scientific interest in the relative mortality between occupation X and the "general population," even after adjustments for differences in distributions by age and gender. Such contrast is of interest only insofar as it addresses, in some sense, the *effect* of occupation X on mortality from disease Y.

What might properly be meant by such an effect? The meaning might be thought to be the difference in mortality (from disease Y) that results from being or not being in occupation X. However, the difference depends on what the unspecified alternative to occupation X actually is. Without any explicit alternative such a concept of effect is of no scientific interest. While the alternative might be identifiable, the usual meaning of the effect of occupation X is that of the effect of a *particular hazard or exposure* (whether it be chemical, physical, psychological, or whatever) occurring in the occupation in question. This conceptualization of an occupational effect is analogous to the meaning of the effect of a drug regimen in a typical clinical trial, the usual concern involving the effect of the drug itself as distinct from its concomitants in the administration of the treatment. Thus the object of an occupational mortality study cannot be the effects of, say, chemical manufacturing, copper smelting, or coke producing, but it can be — and it has been — the effect of occupational exposure to benzene (21), arsenic (1), or coal tar pitch volatiles (15). Only the study of the effects of exposure(s) provides the basis for hygienic improvements and standards.

In terms of thinking of an epidemiologic study as addressing an occurrence relation (17), the object in any occupational mortality study is the relation of a chosen parameter (incidence density, say) of the occurrence of the deaths of interest (due to a particular disease) to occupation — given that the relation reflects the effect of interest, as already discussed. Thus an early concern of study design is to define the compared categories of the determinant — the occupational contrast — in conceptual terms. For this purpose two, already emphasized principles are important: first, that the determinant is to be thought of as an occupational exposure rather than as an occupation per se and, second, that the empirical relation is of interest only insofar as it can be interpreted in causal terms.

Validity of occupational contrast

The contrast of interest in conceptual terms having been defined, the next task is to give it an operational specification. For this purpose the validity concerns have to do with the attainment of the *comparability* of the compared occupations as regards (i) their respective effects, (ii) the populations representing them, and (iii) the accuracy of information on mortality (from the disease at issue) between them.

Comparability of effects

In order for an occupational contrast to reflect the effect of interest, even in a randomized experiment, the following conditions should be met: (i) the index occupation must indeed represent the exposure; (ii) the reference occupation(s) must represent a lesser exposure than the index occupation, if not total nonexposure; and (iii) apart from the effect of the exposure at issue, ie, on the "null hypothesis," the compared occupations must have identical effects on mortality from the disease at issue. The last of these conditions is the counterpart of the therapeutic trial requirements that (i) the "placebo" drug or "sham" operation have no effect of its own and (ii) all extraneous aspects of the treatments in the index and reference groups have, in the aggregate, identical effects on the criterion of outcome.

Example 1. Doll (7) studied the risks of lung and nasal cancers in relation to nickel exposure (conceptually) by contrasting nickel re-

fining to steel making, coal mining, and all other occupations (operationally). The first two of the three needed conditions were readily satisfied, but the third leaves some uncertainty, as is usual. The contrast of nickel refining with all other occupations is the most doubtful because the latter is the least clearly defined reference occupation, and it is difficult for both investigators and readers to judge.

As was already noted, the formulation of the occupational contrast is a matter of designing the scale of the determinant in the occurrence relation that the study is to yield. It deserves careful note that the index occupation (representing the exposure) is compared with expressly selected reference occupations, ie, with only a subcategory of nonexposure that is comparable in effect with the occupation under study.

Comparability of populations

Given an occupational contrast with comparable effects, there is a need to form a study base manifesting the differential effect (attributable to the exposure). In such a base both the exposed and the reference ("placebo") occupation must be represented of course. Moreover the compared populations actually representing them should be such that the expected mortality difference between them, conditional on whatever confounders will be controlled in the analysis, is indeed a reflection of the effect under study.

In occupational mortality studies it is commonplace that only age, gender, race, and calendar time can be controlled directly. In such instances, it is necessary to define the study base so that it is not confounded within the categories defined by these characteristics alone. Therefore, conditional on these characteristics, the compared occupational populations are to have similar mortalities (from the illness of interest) — apart from whatever effect the exposure has. This requirement of comparability of the index (exposed) and reference (nonexposed) populations may be thought of in terms of forces of entry into, and exit from, these populations. A problem can arise only insofar as entry and/or exit is related to the risk of death from the illness of interest (as indicated, eg, by the presence or absence of the illness itself). More specifically, for confounding to be a problem, an indicator of risk must have different implications for the compared populations with respect to entry and/or exit. By the same token, if the compared populations are defined so that such differential selectivity of membership does not occur between them, then they are comparable.

Example 2. Recall example 1 concerning lung cancer mortality in relation to nickel exposure. Even though employees might enter or leave the three occupational populations differentially according to work preference, economic incentives, physical strength, training background, findings in preemployment physical examinations, medical surveillance, health insurance, etc, these factors are unlikely to have any appreciable relation to the risk of death from lung cancer. Thus they are unlikely to jeopardize the comparability of the index and reference populations — conditional on age, gender, and calender time, which were controlled in the analysis.

This comparability-of-populations principle for the design of the study base illustrates again how the exposed are not to be compared with the nonexposed in the aggregate but with an expressly selected subdomain of the latter. The reference population must not only represent a comparable nonexposed occupation, but the population itself must be similar to the index population in terms of extraneous and otherwise uncontrollable determinants of the mortality under study. The selectivity in the formation of the compared subpopulations in the study base is the nonexperimental counterpart of randomization and other aspects of the deliberate assignment of study subjects to the compared categories of the determinant at issue. As was noted, such selectivity is of particular importance in occupational mortality studies due to the common lack of data on potential confounders and the consequent inability to control confounding in the analysis.

Comparability of mortality information

For the compared populations it is necessary to obtain comparable information on the aspect of the mortality under study. In experimental studies the equivalent goal is commonly pursued by the use of double-blind procedures of outcome assessment. In occupational mortality studies it is generally necessary to use routine recordings of deaths and the causes of death as outcome information. The accuracy of such routines can vary according to occupation and can depend on the quality of health services in general, suspicion that the occupation might be responsible for deaths from the cause at issue, concern for insurance and liability, and other factors. Thus it is again necessary to resort to selection as a substitute for control, that is, the use of a study base in which

the compared subpopulations are inherently similar with respect to the accuracy of (routine) information about the deaths of interest.

Comparability of mortality odds

The presented issues of valid contrast are, as has been noted, familiar in experimental research; the three aspects of validity that are pursued through the deliberate and selective formation of occupational contrast are the counterparts of (i) arranging for a suitable "placebo" ("sham") treatment, (ii) randomly allocating the treatments, and (iii) "blinding" informants/observers in regard to the treatment category of any particular subject in the study base.

While these issues of validity are of concern in all studies of occupational mortality, an added problem of validity has to be dealt with in situations in which the source of information is death certificates alone. This problem, which has no familiar counterpart in experimental studies, is not one of valid formation of the study base so that the contrast between its index (exposed) and reference (nonexposed) subdomains truly represents the effect at issue. Instead, it has to do with the validity of information about the contrast in the study base, given that the respective sizes of the compared subdomains of the base must be assessed from death certificates.

The classical way of making use of deaths from other causes is the computation of the proportions that the deaths of interest represent among all deaths in the compared occupational populations (3, 13, 22, 26). Such mortality proportions ("proportionate mortalities") are proportional to the respective mortality rates only on the demanding assumption that the total death rates are the same for the compared populations (3). This problem is avoided by the use of an alternative measure of mortality, the odds of dying of the disease of interest, conditional on dying either of it or of any of the auxiliary (reference) diseases (18).

Such mortality odds are proportional to the respective mortality rates on the condition that the numbers of deaths from the reference diseases involved in the odds are proportional to the respective amounts of population-time between/among the compared population. In other words, the mortality odds is a suitable parameter of outcome for comparative purposes if the incidence rate for the reference deaths is the same for the compared populations (18). This situation again poses a need for selectivity — in this instance as to which other deaths, in terms of disease(s), are to be employed in the auxiliary capacity in the formation of the mortality odds. The two requirements for the reference deaths to be used are:

1. The compared occupations must have identical effects on mortality from the reference disease(s). This condition is satisfied whenever the reference disease(s) are unrelated in their occurrence to all differential exposures between the index and reference occupations.

2. The empirical contrast must be valid with respect to confounding and the comparability of information regarding the reference disease(s) — analogously with the requirements related to mortality from the index disease under study.

Example 3. Consider again the study of lung and nasal cancer mortality in relation to nickel exposure, with those in "all other" occupations as the reference population. Death certificates were the only source of information on the study base (nickel workers plus "all other" workers), and the relative sizes of the compared populations were estimated by the use of deaths due to all other diseases. This procedure was valid insofar as two conditions were met. First, nickel refining and "all other" occupations had to have identical effects on mortality from diseases other than lung and nasal cancer. Second, selection into and out of the compared populations had to be similar with respect to such other mortality, and the detection and certification of these deaths had to be similar between the nickel refiners and the population in "all other" occupations. All of these assumptions are difficult to judge and tenuous by virtue of the use of "all other" occupations and all other deaths.

The "healthy worker effect"

In the literature with which we are familiar, there is no rigorous definition of the "healthy worker effect." This term usually refers to a tendency for any particular employed population to have lower

mortality than the general population. The tendency has been observed for a variety of occupations and causes of death (4, 5, 8, 9, 10, 14, 19, 23, 24). Thus an observed-to-expected (O : E) ratio of less than one might still suggest excess mortality as long as the "general population" is used as the reference population.

This problem is not resolved by any effort to find a universal, nonunity reference value for the O : E ratio [0.9, say, as discussed by Goldsmith (11)]. The reason is that the magnitude of the healthy worker effect is not constant but varies according to many factors, ie, (i) cause of death (4, 5, 8, 9, 10, 14, 16, 19, 23, 24), (ii) demographic factors [It varies by occupation and work category (4, 5, 8, 9, 10, 14, 16, 19, 23, 24, 27), is usually stronger for nonwhites than whites (4, 5, 14, 16) and stronger for the young than for the old (9, 16), generally decreases with early retirement (6, 28), etc.], and (iii) time lag since starting the work or since the zero time of a cohort [It is prominent at the beginning and tends to decline with the passage of time (6, 9, 16, 20, 24, 28).] Quantification of the healthy worker effect specific for such factors also does not seem to provide a general solution to the problem. Rather, the ultimate solution is to rely on proper study designs so that there is no appreciable healthy worker effect to begin with.

As many authors have pointed out, the healthy worker effect arises from the use of the general population as the reference population (6, 8, 9, 10, 11, 14, 16, 19, 20, 23, 24, 27). Each occupational setting has its characteristic requirements and incentives for job entry (2, 6, 8, 9, 10, 14, 16, 19, 20, 24) and exit (2, 6, 9, 10, 14, 16, 20), and these, when different for the index occupation and the "general population" and also when related to mortality, produce the healthy worker effect. By the same token, if the use of the general population is replaced by the use of an occupational population with comparable job entry and exit factors, then there is no healthy worker effect. The healthy worker effect is a reflection of the incomparability of compared *populations* only — a matter of confounding — and it is not a result of the incomparability of the effects or information For the latter types of incomparability, as discussed by Shindell et al (25), the term would be a misleading misnomer.

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