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Work-related diseases — Some problems in study design

by Sven Hernberg, MD¹

HERNBERG S. Work-related diseases — Some problems in study design. *Scand J Work Environ Health* 10 (1984) 367–372. Methodological problems in the epidemiologic study of work-related diseases are addressed. Because the occupational etiologic fraction of work-related diseases is small, its demonstration is often difficult. Especially cross-sectional studies are hampered by diluting effects, such as selection out of an exposed job. The problems involved in the study of four disease groups, ie, chronic nonspecific respiratory disease, musculoskeletal disorders, cardiovascular diseases, and behavioral responses and psychosomatic symptomatology are discussed in some detail.

Key terms: behavioral symptoms, cardiovascular diseases, chronic nonspecific respiratory disease, cross-sectional studies, epidemiologic methods, musculoskeletal disorders, questionnaires.

When a causal relation between an occupational exposure and a specific disease is clear, the disease is defined as occupational, both medically and usually also legally. However, work and work conditions may, in addition, contribute to the development of nonspecific morbidity, either by causation or aggravation or even by indirect influence on the life-style of the worker. Conceptually work-related diseases thus comprise a wide range of morbidity, related in some way or another to occupation, work or work conditions. Classical occupational diseases constitute one end of the continuum, while at the other extreme are disorders with a very slight or uncertain occupational connection. Many of the diseases within the continuum may be work-related under certain conditions only, and their etiology is always multicausal. For example, the main cause of chronic bronchitis is usually cigarette smoking, and there may be no connection at all to work. However, sometimes occupational dust exposure or climatological conditions are contributing factors, and then the same disease can be considered work-related. In this context only work-related diseases that are not generally considered classical occupational diseases will be discussed.

In principle the epidemiologic study of work-related diseases does not differ from epidemiologic research in general. It therefore suffers from the inherent difficulties of all nonexperimental research, eg, in providing evidence for or against the causality of an observed association between two phenomena (4). What is typical, however, is that the occupational

etiologic fraction of a work-related disease is, by definition, comparatively small; in other words, many nonoccupational causes also contribute to the etiology of the disease in question, and sometimes their share is greater than that of the occupational factor. This situation creates problems both for the design of studies on work-related diseases and for the interpretation of the results. Self-evidently, demonstrating the occupational fraction of an etiology of a multifactorial disease becomes more difficult as the fraction decreases. Furthermore, the etiologic fraction can never be generalized because, as a proportion, its magnitude is influenced by the magnitude of all other factors (2). In addition, depending on the exposure intensity, it also varies with time and place. Moreover, the sum of different etiologic fractions often exceeds 100 %, because many causes may not be “sufficient causes” and their effect becomes manifest only in the presence of other causes. The known synergistic interaction between asbestos exposure and cigarette smoking is a good example. Hence it can be said that the lower boundary for the sum of different etiologic fractions is 100 %, whereas the upper boundary can be any figure in excess of 100 % (2).

Research on work-related diseases can focus on different levels of morbidity, ie, on everything from mortality to slight symptoms. The selection of the morbidity indicator depends of course on the problem under study. “Hard” indicators such as death are more reliable than “soft” ones such as subjective symptoms, but they are, on the other hand, crude and fail to reveal the work-relatedness of a number of diseases, such as low-back pain, psychosocial disorders, and, to a great extent, asthma. The optimal “hardness” of the indicator must be determined by the nature of the problem. However, in this context, mortality will not be addressed, partly because

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so much has already been written on the design and interpretation of mortality studies and partly because most of the work-related symptomatology discussed in other presentations of this issue consists of manifestations milder than death.

Although the most informative investigations from the point of view of revealing the work-relatedness of a disease are well-designed longitudinal studies, either cohort or case-referent studies or their hybrids, many of the investigations published thus far on work-related diseases have been cross-sectional, and will probably continue to be so for practical reasons even in the future. Therefore I have considered it pertinent to dwell somewhat on the problems typical for cross-sectional study design, problems which may severely affect validity. The most serious of them, perhaps, is selective turnover from the work in question. The more distressing the subjective job-related symptoms are, the greater the health-based selection involved. And such circumstances yield an underestimate of the true prevalence of the disease. Therefore cross-sectional studies are usually of limited value in proving the work-relatedness of a disease, although they may suggest hypotheses for further study.

Chronic nonspecific respiratory disease

Many occupational exposures affecting the respiratory system cause distinct subjective symptoms which result in a marked health-based selection from the job, the remaining workers representing a "survivor population." That such selection indeed occurs has been intuitive knowledge among practitioners for many years; recently also some scientific studies have documented it as a fact. Especially workers with allergy and chronic obstructive lung disease tend to leave exposed jobs, and some of them may even end up in a study's reference group [see the reports of, eg, Eisen et al (3), Iwao et al (8), and Koskela et al (10)]. Furthermore, plant physicians have long been restrictive in permitting atotics or those with chronic obstructive lung disease to take an "exposed" job. Hence any cross-sectional study of work-related lung diseases tends to underestimate the true prevalence.

Longitudinal studies also suffer from selection bias. Preemployment examination, if successful, may result in a healthier-than-normal exposed group, and selective worker turnover leads to short exposure times for those who are the most affected by subjective symptoms. Many study protocols require a minimum exposure time in order to increase the effectiveness of the investigation, and early dropouts will therefore not become classified as exposed at all. Later dropouts who comply with the minimum exposure criteria pose another type of problem. It is true that they can be found if the tracing procedure is efficient, but they will have experienced less exposure than the "survivor population" and, for that matter, may have even recovered from the initial symptoms.

This possibility, if not controlled, severely distorts the quantitative assessment of the etiologic fraction.

The effect indicators used for studying respiratory diseases usually comprise questionnaires (or interviews), lung function tests, radiographic examinations, and, in some instances, immunologic tests. All these methods pose problems.

Questionnaires and interviews must be well validated to be reliable. Both their specificity and sensitivity should be known. One example of an originally validated method is the British Medical Research Council's bronchitis form, which has gained wide use in epidemiologic studies. However, few researchers realize that this form was validated as an interview, not as a self-administered questionnaire. It was also validated in a country with an exceptionally high prevalence of chronic bronchitis. Furthermore, the original form was in English, but it has later been translated into several other languages. All these circumstances have changed the original situation so that it is highly questionable whether a translated version, used as a self-administered questionnaire in, say, a Scandinavian country with a low prevalence of bronchitis, fulfills the criteria for validation.

Whenever lung function tests are used, it is important to remember exactly what they measure. There is little information to be gained from tests measuring obstruction in the greater airways (forced expiratory volume, forced vital capacity, etc) when the condition under study is mainly a restrictive disorder, eg, fibrosis. In such instances emphasis should be placed on tests measuring diffusion, even though they may be more complicated in field use. Successful measurements of lung function require simple, repeatable tests. Cooperation of the subject is crucial. There is also great interobserver variability, and the same technician should therefore, ideally, perform all the tests. If one technician cannot (eg, too large a study material), the interobserver error must be measured and each of the technicians should examine the same proportion of exposed and reference subjects, even the same proportion of different subcategories of the exposed group. Otherwise an asymmetrical inaccuracy of observations may result, and a severe bias can be created.

The use of roentgenologic examinations is also complicated by inter- and intraobserver errors. Without being perfect, the most recent classification of the International Labour Office (7) is the best method available for the radiographic estimation of fibrosis; hence it should be employed whenever possible. There should be several readers, who should be "blinded" with regard to both the exposure status of the subject and the time sequence of the serial pictures. The inter- and intraobserver errors should be measured and reported.

Another difficult question is how to secure a valid base-line measurement for longitudinal studies. Usually researchers start with a cross-section of cur-

rently employed workers who represent a "survivor population," but who nonetheless probably already have some decrement of function as compared with their own (unknown) values before exposure commenced. The ideal method would be to use a preemployment examination as the base line; this examination then would require better than usual standardization and quality control of the routine lung function test employed, or, even better, an ad hoc program for measuring preexposure values. Serial examinations, combined with the tracing of dropouts (at least the reason for quitting should be recorded), would then give more reliable data than the commonly used approach that I have already mentioned.

No study on occupational respiratory disorders can be valid if smoking is not accounted for. First of all detailed data on past and current smoking habits is required. Next one may wish to consider the approach to be used to ensure that the contrasts between the subcategories are great enough. For example, it may be cost-efficient to focus on heavy smokers and nonsmokers and to omit moderate smokers and exsmokers. Such a procedure requires advance knowledge of smoking habits however. Sometimes information can be obtained from plant health records, but sometimes the smoking status does not become known until the time of the examination. Often the most important information comes from comparisons between exposed and nonexposed heavy smokers, because the exposure under study and smoking may act synergistically. In other instances the effect of smoking upon some parameter (eg, closing volume) may be so overwhelming that the occupational etiologic fraction cannot be identified. Then comparisons of nonsmokers will yield the best information. How to classify exsmokers can pose a problem. Sometimes they can be classified as nonsmokers (provided some time, a year or two, has elapsed), but sometimes the effect of smoking is more irreversible, eg, when emphysema is concerned. One should also remember that some health-related cause may have been the reason for the exsmoker's quitting. If the study material is sufficiently large, exsmokers should perhaps be left out completely.

Musculoskeletal disorders

The study of musculoskeletal disorders, especially of low-back pain, poses several difficult problems. Because low-back pain is indeed painful, it causes highly selective turnover for work with demands on the spine. Such selection invalidates most or all cross-sectional studies, especially since less demanding tasks, often used for contrast, by no means exert such selective power. Hence, in a cross-sectional study, mere selection (and lack of it or selection with an opposite direction in the reference group) can totally mask work-related low-back pain. It is true that, in spite of this fact, many authors have shown an ex-

ceptionally high frequency of low-back pain in connection with demanding tasks, but such findings must reflect "endurable" disorders, not the more severe manifestations, and especially not those leading to incapacity.

Selection is a problem in longitudinal studies also because those with the worst manifestations tend to quit too early to become classified as having "heavy" or "long-term" exposure. From a practical viewpoint a high turnover also creates difficulties in tracing all members of the study population. Finally, causation and aggravation are often difficult, if at all possible, to differentiate between, a problem which hampers etiologic research in particular.

Another type of problem arises from difficulties in assessing life-long history of "exposure." In real life the "exposure" of the back to various types of trauma, strain, and stress is usually very long and diversified. Standardized "exposure" ratings have not been developed, and even if they existed, the memory of the subjects would probably not be accurate enough to account for a life's history of "exposures." While some "exposures," such as trauma, may cause immediate effects (trauma of course can also initiate later effects), others such as whole-body vibration may cause symptoms after a long period of latency. Other "exposures," such as lifting, may or may not have latency periods before chronic low-back pain results. Often there are combinations of different "exposures," and, to complicate matters even more, occupational "exposures" are frequently confounded by leisure-time "exposures" such as sports injuries, strain during holiday gardening, etc. In addition, both work and, especially, leisure-time activities, if physiological, can have beneficial effects. This complicated pattern indeed renders the assessment of occupational "exposure" a hard task.

The effect side also presents problems. Low-back pain is a variety of different disorders rather than a single entity (12). A prolapsed lumbar disc may have quite another etiology than, eg, spondylosis, muscle spasms, or inflammatory processes. The diagnostic procedures used to differentiate each syndrome are complicated even in clinical examinations of single patients, not to speak of epidemiologic series comprising hundreds or thousands of subjects. For example, Kersley (9) found it impossible to classify more than 60 % of a series of 404 patients with chronic back pain, even in a thorough examination. Follow-up studies in particular would require simple and reliable tests, not only for discriminating between the various syndromes causing low-back pain, but also for providing repeatable assessments of the back's condition. Such tests do not exist. Ethical considerations often prevent the use of certain examinations, eg, radiographic examinations, for clinically symptomless subjects. In case-referent studies, where the number of patients is far smaller, more elaborate examinations can be used, and ethical

restrictions are fewer because "cases" are ill. Nevertheless follow-up studies can hardly afford to devote more than 10 to 15 min to each subject, and all tests must be completely safe. A serious problem is also the lack of good parameters for measuring a condition quantitatively. For example, in osteoarthritis, mobility measurements and radiographic examinations are often conflicting, as Videman (15) has shown in an experimental study on rabbits. While the radiographic findings steadily deteriorated, morbidity and the macroscopic anatomic findings did not always worsen.

Finally, there are great constitutional differences between subjects. These dissimilarities include (i) macroanatomic features such as the size of the spinal canal, bony anomalies, etc; (ii) differences between the different collagens (there are about 120 types) and the composition of the glycosaminoglycans; (iii) natural motor skill; (iv) muscular strength (the effects of which may act in two directions because very strong muscles are not always beneficial); and (v) psychological factors such as the degree of risk-taking, neuroticism, etc. These factors, alone or together, often result in variation with effects that can be much greater than that of the "exposure" under study, ie, occupational factors.

These considerations should, however, not hinder the planning and implementation of sound studies. They should serve though to indicate how difficult the problem often is and how many aspects there are that must be taken care of. They should furthermore warn against drawing too far-reaching conclusions from studies that are not perfect. And they should, perhaps, discourage the initiation of studies which, from the very beginning, are doomed to fail. Therefore, without presenting a recommendation for a perfect study protocol, the preceding discussion will hopefully help potential investigators analyze their specific situation to see if they can overcome at least the major pitfalls of the epidemiologic study of musculoskeletal disorders.

Cardiovascular diseases

Cardiovascular diseases have been studied epidemiologically more than any other disease group. Hence cardiovascular epidemiology has served as a model for the epidemiologic study of chronic diseases in general. However, most of the work done concerns the natural history of cardiovascular diseases, and the impact of occupational factors has not always been sufficiently considered. Longitudinal studies of the effects of some cardiotoxic agents, such as carbon disulfide and nitroglycol, have provided the most thorough considerations of the methodology from the point of view of occupational epidemiology (5, 6, 14).

The great experience with cardiovascular epidemiology in general has helped the design of valid studies

on occupationally-related problems too. Especially knowledge of the relative importance of the "heavy" risk factors smoking, hypertension, and hyperlipemia, as well as of others such as diabetes, physical inactivity, gout, etc, helps the control of potential confounders in a study on work-related cardiovascular mortality. The better the control of the nonoccupational factors, the greater the sensitivity of a study to detect occupational factors. However, in this context, a warning must be given against overmatching on intermediates in the etiologic chain, a procedure which leads to the masking of a true effect. For example, in our study on the effects of carbon disulfide exposure on cardiovascular morbidity, we did not control blood pressure and the cholesterol level because elevated values of both had been suggested as the mechanisms by which carbon disulfide would increase coronary morbidity (5). But, irrespective of such considerations, any study on cardiovascular morbidity requires measurements of all important risk factors in addition to the occupational factor under study, and this requirement increases costs.

Selection is another problem, as almost always in occupational epidemiology. Cardiovascular diseases are known to cause a strong "healthy worker effect" in morbidity studies (11), partly because early symptoms may force the workers to quit or, primarily, seek a lighter job and partly because it is possible to identify high-risk individuals at an early stage. Such persons may not be hired, or they may selectively become unemployed, especially during periods of economic depression. It is obvious that not only mortality becomes affected, but also milder manifestations, especially angina. Therefore, if possible, a reference group should be sought in which the same types of selective forces operate.

Occupational factors in the causation of cardiovascular disease may be direct, such as toxic exposures, work stress, and perhaps noise, cold and heat, or indirect, such as excessive smoking in some occupations, sedentary work in others, bad dietary habits in still others, etc. In each case a thorough understanding of the underlying mechanisms is a prerequisite. Depending on the "Fragestellung," these indirectly acting factors can either be treated as occupational risk factors or as confounders.

Cardiovascular morbidity can be measured from a long range of indicators of different "hardness," starting with risk factors such as hypertension or hyperlipemia and ending with mortality. Especially the questionnaire on angina by the World Health Organization has gained wide use (16). Likewise, hardly any morbidity study would consider leaving out electrocardiography, either at rest or after standardized exercise. Blind coding of electrocardiographic changes, especially those indicating past infarction or ischemia, according to the so-called Minnesota code (1), has been recommended during the last two

decades. Although individual diagnoses cannot be made on the basis of isolated electrocardiographic findings only, this method — which employs technicians as coders — takes care of observer bias and ensures an objective reading by eliminating more or less well-founded “clinical impressions.”

The selection of morbidity parameters in cardiovascular surveys is not guided only by scientific considerations. The vast amount of cardiological examination methods available tempts the investigator to use several tests, preferably modern and sophisticated ones, on one hand, while restrictions of funds and the limited availability of technicians act inhibitingly on the other. One has to be selective. In this process it is crucial to ponder thoroughly exactly what new information might be gained from each of the alternative tests. For example, increasing the sensitivity of electrocardiographic examinations with the use of a maximal exercise test may sharpen the study in some instances, but it may not yield anything new at all in others, while at the same time creating a vast amount of extra work. In our study on cardiovascular morbidity among workers exposed to carbon disulfide the inclusion of exercise electrocardiography did not introduce information that would not have been gained from less sensitive parameters (5). However, this wisdom did not emerge until the data analysis — knowing in advance what exactly each examination will yield is not so simple.

Compared with other work-related cardiovascular problems, the study of toxic effects is relatively straightforward. More subtle aspects are discussed next.

Behavioral responses and psychosomatic symptomatology

Research on behavioral responses and psychosomatic symptomatology has usually been cross-sectional, and it generally relies on the use of interviews and questionnaires, ie, the softest of methods. These techniques are valid only in the hands of skilled and insightful researchers. The danger lies in the fact that their use is so seemingly simple that also dilettantes are tempted to employ them. Most situations giving rise to behavioral symptomatology, be it aggressiveness, depression, insomnia, or psychosomatic diseases such as hypertension or peptic ulcer, are so full of emotional conflicts that unbiased responses to the questions may be difficult to obtain. Because the general social environment also has a great impact on the whole of an individual, it is always necessary to incorporate many questions relating to the general life situation into all surveys on occupational risks. This necessity adds to the demands on the qualifications of the investigator, greatly increases the number of test variables, and, thereby, also renders the questionnaires/interviews laborious to administer and cumbersome to analyze.

The effect variables are also often diffuse and nonspecific, and therefore strictly standardized and validated diagnostic criteria are required. Reliable diagnostics can be achieved for “heavy” endpoints such as coronary infarction, suicide, or peptic ulcer, but milder manifestations such as insomnia, headache, vertigo, etc, can be very hard or impossible to define in a valid and concise way. Furthermore, the causal chain from exposure to effect is not always straightforward. Sometimes, eg, work stress may first cause overconsumption of tobacco and alcohol. This reaction can be considered an “effect” as such, but it can also indirectly (from the point of view of stress) cause increased morbidity in, say, cardiovascular or gastrointestinal disorders. Such complicated interactions must be understood well before any study is initiated, and allowance for such circumstances must, if possible, be given both at the planning stage (collection of enough information, enough contrasts between subgroups) and at the data analysis stage (sophisticated multivariate statistical methods).

Whenever “objective” methods of assessing the psychological work load are available, eg, the German so-called AET method (13), they should be used. For example, factors such as the level of the work demands, the number of stimuli, the repetitiveness of the tasks, the degree of control over the work situation, etc, can be measured. But, usually, subjective assessments of the work situation and its effects, apart from frank clinical manifestations, are the main source of information because many work “exposures,” such as social interaction, are not at all measurable objectively.

The choice of a valid reference group is especially difficult in psychosocial epidemiology where many background variables outside the work situation must always be controlled. There are many unpredictable social changes in human life that may affect the group in question and their referents in different ways, the result being a distortion of an initially sound comparison, especially in a study with a longitudinal design. From a practical viewpoint it may be impossible to collect all the relevant background data before the groups are formed, and controlling confounding then becomes a problem for the data analysis stage. But without detailed information on potential confounders this type of control is not possible.

Selection is also problematic in psychosocial studies. Most people choose their occupation on psychological grounds, such as motivation, personality, initial intellectual or psychomotor capacity, etc. Such aspects are far more important at the time of *job entry* than the health-based selection. In the same manner selection through *job termination* often depends on psychological factors, although the importance of medical aspects now becomes greater. Finding a reference group for which the forces of se-

lection are similar with respect to both job entry and job termination can often prove to be an impossible task.

Employing intraindividual comparisons overcomes some of the problems mentioned, but this approach requires a longitudinal design, with or without an intervention. Furthermore, a before-after evaluation can introduce other biases, and therefore a reference group is usually required. Prospective, longitudinal studies, although also struggling against uncontrollable bias, give in general more reliable data than cross-sectional ones, but the costs can easily become formidable because repeated measurements of a great number of variables are required. Furthermore, because of predicted loss of material due to drop-outs, the initial study groups must be much larger than actually needed to measure an effect. Hence feasibility aspects can make a prospective design impossible.

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